

CC #2



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AMINO ACID DERIVATIVE ANTICONVULSANT

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The present invention relates to compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders. More specifically, the compounds of this invention can be characterized as protected amino acid derivatives of the formula:



I

10

or the N-oxides thereof or pharmaceutically acceptable salts thereof wherein

15

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

20

R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

25

R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, SO₃⁻ or Z-Y wherein R₂ and R₃ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

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V

1 Z is O, S, S(O)_a, NR₄, PR₄ or a chemical bond;
Y is hydrogen, lower alkyl, aryl, aryl lower
alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic,
5 heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower
alkyl and Y may be unsubstituted or substituted with an
electron donating group or an electron withdrawing group,
provided Z is a chemical bond only, when Y is halo, or

ZY taken together is NR₄NR₅R₇, NR₄OR₅, ONR₄R₇,
OPR₄R₅, PR₄OR₅, SNR₄R₇, NR₄SR₇, SPR₄R₅, PR₄SR₇, NR₄PR₅R₆

10 PR₄NR₅R₇, $\begin{matrix} \text{NR}_4\text{C}-\text{R}_5 \\ \parallel \\ \text{O} \end{matrix}$, SCR₅, $\begin{matrix} \text{NR}_4\text{C}-\text{OR}_5 \\ \parallel \\ \text{O} \end{matrix}$, SC-OR₅, $\begin{matrix} \text{NR}_4\text{C}-\text{NR}_5\text{R}_6 \\ \parallel \\ \text{O} \end{matrix}$,

T30X $\begin{matrix} \text{NR}_4\text{CNR}_5\text{S(O)}_a\text{R}_6 \\ \parallel \\ \text{O} \end{matrix}$, $\begin{matrix} \text{NR}_4\text{CNR}_5\text{R}_6 \\ \parallel \\ \text{S} \end{matrix}$, $\begin{matrix} \text{NR}_4\text{CMNR}_5\text{COR}_6 \\ \parallel \\ \text{Q} \end{matrix}$, $\begin{matrix} \parallel \\ \text{A} \end{matrix}$, $\begin{matrix} \text{C}-\text{NH}_2 \\ \parallel \\ \text{S} \end{matrix}$

15 R₄, R₅ and R₆ are independently hydrogen, lower
alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower
alkynyl, wherein R₄, R₅ and R₆ may be unsubstituted or
substituted with an electron withdrawing group or an
electron donating group and

20 R₇ is R₆ or COOR₈ or COR₈

R₈ is hydrogen or lower alkyl, or aryl lower
alkyl, and the aryl or alkyl group may be unsubstituted or
substituted with an electron withdrawing group or an
electron donating group and

25 A and Q are independently O or S, M is an
alkylene chain containing up to 6 carbon atoms or a
chemical bond;

n is 1-4 and

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1 a is 1-3.

5 The predominant application of anticonvulsant drugs
is the control and prevention of seizures associated with
epilepsy or related central nervous system disorders. Epilepsy
refers to many types of recurrent seizures produced by
paroxysmal excessive neuronal discharges in the brain; the two
main generalized seizures are petit mal, which is associated
with myoclonic jerks, akinetic seizures, transient loss of
consciousness, but without convulsion; and grand mal which
manifests in a continuous series of seizures and convulsions
10 with loss of consciousness.

15 The mainstay of treatment for such disorders has been
the long-term and consistent administration of anticonvulsant
drugs. Most drugs in use are weak acids that, presumably,
exert their action on neurons, glial cells or both of the
central nervous system. The majority of these compounds are
characterized by the presence of at least one amide unit and
one or more benzene rings that are present as a phenyl group or
part of a cyclic system.

20 Much attention has been focused upon the development
of anticonvulsant drugs and today many such drugs are well
known. For example, the hydantions, such as phenytoin, are
useful in the control of generalized seizures and all forms of
partial seizures. The oxazolidinediones, such as trimethadione
25 and paramethadione, are used in the treatment of nonconvulsive
seizures. Phenacemide, a phenylacetylurea, is one of the most
well known anticonvulsants employed today, while much attention
has recently been dedicated to the investigation of the
diazepines and piperazines. For example, U.S. Patent Nos.
30 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified
diazepine derivatives useful in the treatment of epilepsy and
other nervous disorders. U.S. Patent No. 3,887,543 to
Nakanishi, et al. describes a thieno [2,3-e][1,4] diazepine

1 compound also having anticonvulsant activity and other
depressant activity. U.S. Patent No. 4,209,516 to Heckendorf,
et al. relates to triazole derivatives which exhibit
anticonvulsant activity and are useful in the treatment of
epilepsy and conditions of tension and agitation. U.S. Patent
5 No. 4,372,974 to Fish, et al. discloses a pharmaceutical
formulation containing an aliphatic amino acid compound in
which the carboxylic acid and primary amine are separated by
three or four units. Administration of these compounds in an
acid pH range are useful in the treatment of convulsion
10 disorders and also possess anxiolytic and sedative properties.

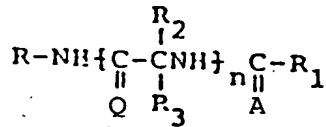
15 Unfortunately, despite the many available
pharmacotherapeutic agents, a significant percentage of the
population with epilepsy or related disorders are poorly
managed. Moreover, none of the drugs presently available are
capable of achieving total seizure control and most have
disturbing side-effects. Clearly, current therapy has failed
to "seize control" of these debilitating diseases.

20 It is therefore one object of the present invention
to provide novel compounds exhibiting CNS activity,
particularly anticonvulsant activity.

25 Another object of this invention is to provide
pharmaceutical compositions useful in the treatment of epilepsy
and other CNS disorders.

30 A further object of this invention is to provide a
method of treating epilepsy and related convulsant disorders.

These and other objects are accomplished herein by
providing compounds of the following general formula:



1 wherein R, R₁, R₂, R₃, R₄, R₅, R₆, n, Z, Y, A and Q are as
defined hereinabove.

5 The present invention contemplates employing the
compounds of Formula I in compositions of pharmaceutically
acceptable dosage forms. Where the appropriate substituents
are employed, the present invention also includes
pharmaceutically acceptable addition salts. Moreover, the
administration of an effective amount of the present compounds,
10 in their pharmaceutically acceptable forms or the addition
salts thereof, can provide an excellent regime for the
treatment of epilepsy, nervous anxiety, psychosis, insomnia and
other related central nervous disorders.

15 The alkyl groups when used alone or in combination
with other groups, are lower alkyl containing from 1 to 6
carbon atoms and may be straight chain or branched. These
groups include methyl, ethyl, propyl, isopropyl, butyl,
isobutyl, tertiary butyl, amyl, hexyl, and the like.

20 The aryl lower alkyl groups include, for example,
benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, and
the like, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenyl-
ethyl, and the like.

25 The term aryl, when used along or in combination,
refers to an aromatic group which contains from 6 up to 18 ring
carbon atoms and up to a total of 25 carbon atoms and includes
the polynuclear aromatics. These aryl groups may be
monocyclic, bicyclic, tricyclic or polycyclic and are fused
rings. Polynuclear aromatic compound is meant to encompass
bicyclic, tricyclic fused aromatic ring system containing from
10-18 ring carbon atoms and up to a total of 25 carbon atoms.
30 The aryl group includes phenyl, and the polynuclear aromatics
e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and the
like. The aryl group also includes groups like ferrocenyl.

1 Lower alkenyl is an alkenyl group containing from 2
to 6 carbon atoms and at least one double bond. These groups
may be straight chained or branched and may be in the Z or E
form. Such groups include vinyl, propenyl, 1-butenyl,
5 isobut enyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl,
(E)-2-pentenyl, (Z)-4-methyl-2-pentenyl,
(E)-4-methyl-2-pentenyl, pentadienyl, e.g., 1,3 or 2,4-
pentadienyl, and the like.

10 The term alkynyl include alkyne substituents
containing 2 to 6 carbon atoms and may be straight chained as
well as branched. It includes such groups as ethynyl,
propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl,
3-methyl-1-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl,
15 3-hexynyl and the like.

20 The term cycloalkyl when used alone or in combination
is a cycloalkyl group containing from 3 to 18 ring carbon atoms
and up to a total of 25 carbon atoms. The cycloalkyl groups
may be monocyclic, bicyclic, tricyclic, or polycyclic and the
rings are fused. The cycloalkyl may be completely saturated or
partially saturated. Examples include cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl,
cyclohexenyl, cyclopentenyl, cyclooctenyl, cycloheptenyl,
decalinyl, hydroindanyl, indanyl, fenchyl, pinenyl, adamantlyl,
25 and the like. Cycloalkyl includes the cis or trans forms.
Furthermore, the substituents may either be in endo or exo
positions in the bridged bicyclic systems.

30 The term "electron-withdrawing and electron donating"
refer to the ability of a substituent to withdraw or donate
electrons relative to that of hydrogen if the hydrogen atom
occupied the same position in the molecule. These terms are
well understood by one skilled in the art and are discussed in
Advanced Organic Chemistry, by J. March, John Wiley and Sons,
New York NY, pp. 16-18 (1985) and the discussion therein is

1 incorporated herein by reference. Electron withdrawing groups
include halo, including bromo, fluoro, chloro, iodo and the
like; nitro, carboxy, lower alkenyl, lower alkynyl, formyl,
carboxyamido, aryl, quaternary ammonium, trifluoromethyl, aryl
lower alkanoyl, carbalkoxy and the like. Electron donating
5 groups include such groups as hydroxy, lower alkoxy, including
methoxy, ethoxy and the like; lower alkyl, such as methyl,
ethyl, and the like; amino, lower alkylamino, di(loweralkyl)
10 amino, aryloxy such as phenoxy, mercapto, lower alkylthio,
lower alkylmercapto, disulfide (lower alkylthio) and the
like. One skilled in the art will appreciate that the
aforesaid substituents may have electron donating or electron
15 withdrawing properties under different chemical conditions.
Moreover, the present invention contemplates any combination of
substituents selected from the above-identified groups.

15 The term halo includes fluoro, chloro, bromo, iodo
and the like.

The term acyl includes lower alkanoyl.

20 As employed herein, the heterocyclic substituent
contains at least one sulfur, nitrogen or oxygen, but also may
include one or several of said atoms. The heterocyclic
substituents contemplated by the present invention include
heteroaromatics and saturated and partially saturated
25 heterocyclic compounds. These heterocyclics may be monocyclic,
bicyclic, tricyclic or polycyclic and are fused rings. They
may contain up to 18 ring atoms and up to a total of 17 ring
carbon atoms and a total of up to 25 carbon atoms. The
heterocyclics are also intended to include the so-called
benzoheterocycles. Representative heterocyclics include furyl,
30 thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl,
oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl,
piperazinyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl,
benzfuryl, benzothienyl, morpholinyl, benzoxazolyl,

1 tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl,
pyrazolidinyl, imidazolinyl, imadazolidinyl, pyrrolidinyl,
furazanyl, N-methylindolyl, methylfuryl, pyridazinyl,
pyrimidinyl, pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl,
5 azetidinyl, the N-oxides of the nitrogen containing
heterocycles, such as the nitric oxides of pyridyl, pyrazinyl,
and pyrimidinyl and the like. The preferred heterocyclic are
thienyl, furyl, pyrrolyl, benzofuryl, benzothienyl, indolyl,
methylpyrrolyl, morpholinyl, pyridyl, pyrazinyl, imidazolyl,
10 pyrimidinyl, pyrazolyl or pyridazinyl. The preferred
heterocyclic is a 5 or 6-membered heterocyclic compound.
The especially preferred heterocyclic is furyl, pyridyl,
pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl,
oxadiazolyl, epoxy, pyrimidinyl, or pyridazinyl. The most
15 preferred heterocyclics are furyl, pyrazolyl, pyrrolyl and
pyridyl. The preferred compounds are those wherein n is 1, but
di, tri and tetrapeptides are also contemplated to be within
the scope of the claims.

20 The preferred values of R is aryl lower alkyl,
especially benzyl, and the preferred R_1 is H or lower alkyl.
The most preferred R_1 group is methyl.

25 The most preferred electron donating substituent and
electron withdrawing substituent are halo, nitro, alkanoyl,
formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy,
carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic,
guanidine, quaternary ammonium, lower alkenyl, lower alkynyl,
sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino,
lower alkylamino, di(loweralkyl)amino, amino lower alkyl
mercupto, mercaptoalkyl, alkylthio; and alkylidithio. The term
30 "sulfide" encompasses mercapto, mercapto alkyl and alkylthio,
while the term disulfide encompasses alkylidithio. These
preferred substituents may be substituted on any one of R_1 , R_2 ,
 R_3 , R_4 , R_5 or R_6 , R_7 or R_8 as defined herein.

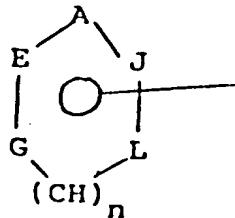
1 The ZY groups representative of R₂ and R₃ include hydroxy, alkoxy, such as methoxy, ethoxy, aryloxy, such as phenoxy; thioalkoxy, such as thiomethoxy, thioethoxy; thioaryloxy such as thiophenoxy; amino; alkylamino, such as methylamino, ethylamino; arylamino, such as anilino; lower dialkylamino, such as, dimethylamino; trialkyl ammonium salt, hydrazino, alkylhydrazino and arylhydrazino, such as N-methylhydrazino, N-phenylhydrazino, carbalkoxy hydrazino, aralkoxycarbonyl hydrazino, aryloxycarbonyl hydrazino, hydroxylamino, such as N-hydroxylamino (-NH-OH), lower alkoxy amino [(NHOR₁₈) wherein R₁₈ is lower alkyl], N-lower alkylhydroxyl amino [(NCR₁₈)OH wherein R₁₈ is lower alkyl], N-lower alkyl-O-lower alkyl hydroxyamino, i.e., [N(R₁₈)OR₁₉] wherein R₁₈ and R₁₉ are independently lower alkyl] and o-hydroxylamino (-O-NH₂); alkylamido such as acetamido, trifluoroacetamido, lower alkoxyamino, (e.g. NH(OCH₃)); and heterocyclicamino, such as pyrazoylamino.

20 Furthermore, in still another embodiment Z may be O, S, NR₄ or PR₄ and Y may be hydrogen, lower alkyl or aryl and R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, n and a are as defined hereinabove.

T(100)
25 In a still further embodiment, ZY may be NR_4CR_5 ,
 or SCR_5 or $\text{NR}_4\overset{\parallel}{\underset{\text{O}}{\text{C}}}\text{-OR}_5$, or $\text{SC}\overset{\parallel}{\underset{\text{O}}{\text{-}}} \text{OR}_5$ and
 R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, n and a are as defined hereinabove.

30 When R₂ or R₃ is heterocyclic, the preferred heterocyclics are furyl, tetrahydrofuryl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl or epoxy. The most preferred heterocyclic is furyl, pyridyl, pyrazoyl and pyrrolyl.

The preferred heterocyclic groups representative of R_2 and R_3 have the formula



XII

or those corresponding partially or fully saturated form thereof wherein n is 0 or 1

A, Z, L and J are independently CH, or a heteroatom selected from the group consisting of N, O, S and

G is CH, or a heteroatom selected from the group consisting of N, O and S.

but when n is O, G is CH, or a heterocyclic selected from the group consisting of NH, O and S with the proviso that at most two of A, E, L, J and G are heteroatoms.

If the ring depicted hereinabove contains a nitrogen ring atom, then the N-oxide forms are also contemplated to be within the scope of the invention.

When R_2 or R_3 is a heterocyclic of the above formula, it may be bonded to the main chain by a ring carbon atom. When n is 0, R_2 or R_3 may additionally be bonded to the main chain by a nitrogen ring atom.

R_2 or R_3 may independently also be SO_3^- , or

Furthermore, ZY may also be $\overset{\sim}{\text{NR}_4}\text{C} \underset{\text{O}}{\underset{\parallel}{\text{NR}_5\text{R}_6}}$,

$$\text{NR}_4^{\text{CNR}_5\text{S(O)aR}_6}, \quad \text{NR}_4^{\text{C-NR}_5\text{R}_6}, \quad \text{C} = \text{NH}_2 \text{ or}$$

$$\text{or } R_4 \underset{\substack{\parallel \\ Q}}{\text{CM}} NR_5 \underset{\substack{\parallel \\ A}}{\text{C}} OR_6.$$

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1 When R_2 is alkenyl the alkenyl group is a lower
alkenyl group having 1-6 carbon atoms. The alkenyl group
may be substituted with an electron donating group and more
preferably with an electron withdrawing group, such as
5 COOH.

10 As indicated hereinabove, Q and A may be O or S;
in other words, the main chain may contain only C=O, only
-C=S or combinations thereof. All such permutations are
contemplated herein. It is preferred that the compounds of
the present invention contain no more than 2 C=S moieties,
it is even more preferred that the compounds of the present
invention contain no more than 1 C=S moiety. The most
preferred embodiment are when A and Q are both oxygen.

15 An embodiment of the present application is one
in which the compounds are of Formula I wherein R is lower
cycloalkyl or lower cycloalkyl lower alkyl, and R is
unsubstituted or is substituted with at least one electron
withdrawing group or electron donating group and R_1 , R_2 ,
 R_3 , Z, Y or ZY taken together, R_4 , R_5 , R_6 , R_7 , R_8 , n and a
20 are as defined herein.

25 Another embodiment of the present invention
include compounds of Formula I wherein R_1 is lower
cycloalkyl or lower cycloalkyl lower alkyl and R_1 may be
unsubstituted or substituted with an electron donating
group or electron withdrawing group and R_1 , R_2 , R_3 , Z, Y,
or ZY taken together, R_4 , R_5 , R_6 , R_7 , R_8 n and a are as
defined hereinabove.

1 Another embodiment of the present invention
includes compounds of Formula I wherein R₂ is lower
cycloalkyl or lower cycloalkyl lower alkyl and R₂ may be
unsubstituted or substituted with an electron donating
5 group or electron withdrawing group, and R, R₁, R₃, R₄, R₅,
R₆, R₇, R₈ and a are as defined hereinabove.

10 Still another embodiment of the present invention
include compounds of Formula I wherein R₃ is lower
cycloalkyl or lower cycloalkyl lower alkyl and R₃ may be
unsubstituted or substituted with an electron donating or
15 electron withdrawing group and R, R₁, R₂, R₄, R₅, R₆, R₇,
R₈, n and a are as defined hereinabove.

A further embodiment of the present invention
include compounds of Formula I wherein Z is S(O)_a and R,
15 R₁, R₂, R₃, Y, R₄, R₅, R₆, R₇, R₈, n and a are as defined
herein.

It is preferred that one of R₂ and R₃ is hydrogen.

In a preferred embodiment, one of R₂ and R₃ is
hydrogen and that the other is heterocyclic. It is preferred
that one of R₂ and R₃ is a heterocyclic having Formula XI. The
preferred heterocyclics include furyl, thieryl, benzothienyl,
benzofuryl, oxazolyl, thiazolyl, isoxazolyl, indolyl,
pyrazolyl, isoxazolidinyl, benzothienyl, benzofuryl,
morpholinyl, indolyl, pyrrolyl, furfuryl, and methyl-
25 pyrrolyl, pyridyl, pyrazinyl, imidazolyl, pyrimidinyl or
pyridazinyl, pyrazolyl, or epoxy. In another preferred
embodiment, one of R₂ and R₃ is alkyl (e.g.
methylisopropyl), aryl (e.g., phenyl), ~~2-thiomethylethyl,~~
~~lower alkoxy (e.g., phenyl), 2-thiomethylethyl,~~ lower
30 alkoxy (e.g., ethoxy, methoxy), anilino, propenyl,

D
A
B
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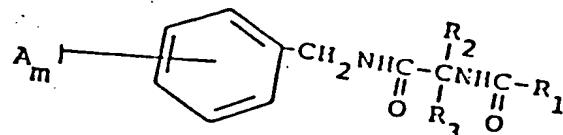
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alkylamino (e.g., ethylamino or methylamino). In another preferred embodiment, one of R₂ and R₃ is hydrogen and the other is heterocyclic lower alkyl, lower alkenyl, amino, lower alkoxy amino, N-lower alkylhydroxyamino, lower alkoxyamino, N-lower alkyl-O-lower alkylhydroxyamino or aralkoxycarbonylhydrazino.

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Preferred compounds of the present invention have the following general formula:

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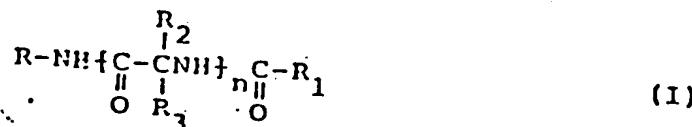


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wherein R₁ is H or lower alkyl, R₂ and R₃ are as defined above and A is hydrogen or an electron donating group or electron-withdrawing group and m is 0-5. It is preferred that A is hydrogen (i.e., m=0). However, values of m equalling 1, 2 or 3 are also preferred.

25

Preferred embodiments include compounds of Formula I



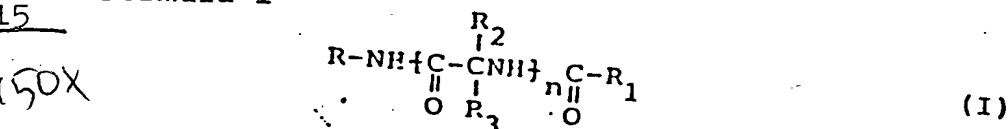
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1 wherein R and R₁, independently, are hydrogen, lower alkyl,
lower alkenyl, lower alkynyl, aryl lower alkyl, aryl,
heterocyclic, lower alkyl heterocyclic, each unsubstituted or
substituted with at least one substituent;

5 R₂ and R₃, independently, are hydrogen, lower alkyl,
lower alkenyl, lower alkynyl, aryl lower alkyl, aryl,
heterocyclic, lower alkyl heterocyclic, each unsubstituted or
substituted with at least one substituent; halogen or a
10 heteroatom containing oxygen, nitrogen, sulfur or phosphorous
substituted with hydrogen, lower alkyl or aryl, said lower
alkyl or aryl groups being substituted or unsubstituted; and
n is 1 to 4.

Another preferred embodiment is a compound having
Formula I



wherein R is aryl, aryl lower alkyl, heterocyclic, lower alkyl
20 heterocyclic, polynuclear aromatic or lower alkyl polynuclear
aromatic, each unsubstituted or substituted with at least one
electron withdrawing substituent or at least one electron
donating substituent;

R₁ is H or lower alkyl, unsubstituted or substituted

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1 with at least one electron withdrawing substituent or at least
one electron donating substituent;

5 R_2 and R_3 , independently, are hydrogen, lower alkyl,
lower alkenyl, lower alkynyl, aryl, aryl lower alkyl,
heterocyclic, lower alkyl heterocyclic, polynuclear aromatic,
lower alkyl polynuclear aromatic, each unsubstituted or
substituted with at least one electron donating substituent,
halogen or a heteroatom containing oxygen, nitrogen, sulfur or
phosphorous substituted with hydrogen, lower alkyl or aryl,
said lower alkyl or aryl groups being substituted or
10 unsubstituted; and

n is 1 to 4.

Another preferred embodiment of the present invention
is a compound of Formula I



wherein R is aryl lower alkyl, heterocyclic, lower alkyl
20 heterocyclic, polynuclear aromatic or lower alkyl polynuclear
aromatic, each of which may be unsubstituted or substituted
with at least one halo, nitro, acyl, carboxyl, carboalkoxy,
carboxamide, cyano, sulfonyl, sulfoxide (sulfinyl),
heterocyclic, guanidine, quaternary ammonium hydroxy, alkoxy,
alkyl, amino, phenoxy, mercapto, sulfide or disulfide;

25 R_1 is H or lower alkyl which may be unsubstituted or
substituted with at least one halo, nitro, acyl, carboxamide,
cyano, sulfonyl, sulfoxide (sulfinyl), heterocyclic, guanidine,
quaternary ammonium, hydroxy, lower alkoxy, amino, phenoxy,
sulfide, or disulfide;

30 R_2 is hydrogen, lower alkyl, lower alkenyl, lower
alkynyl, aryl, heterocyclic, lower alkyl heterocyclic,
polynuclear aromatic, lower alkyl polynuclear aromatic, each

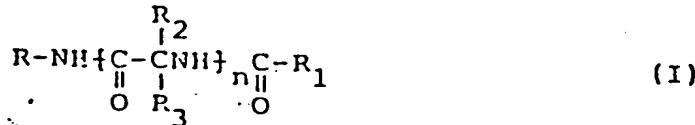
1 unsubstituted or substituted with at least one electron
 withdrawing substituent or at least one electron donating
 substituent; halogen or a heteroatom consisting of oxygen,
 nitrogen, sulfur or phosphorous, said heteroatom being
 substituted with hydrogen, lower alkyl or aryl, said lower
 alkyl or aryl groups being substituted or unsubstituted;

5 R₃ is hydrogen, lower alkyl, lower alkenyl, lower
 alkynyl, aryl, heterocyclic, lower alkyl heterocyclic,
 polynuclear aromatic, lower alkyl polynuclear aromatic, each
 unsubstituted or substituted with at least one electron
 withdrawing substituent or at least one electron donating
 substituent; halogen or a heteroatom consisting of oxygen,
 nitrogen, sulfur, or phosphorous said heteroatom being
 substituted with hydrogen, lower alkyl or aryl, said lower
 alkyl or aryl groups being substituted or unsubstituted;

10 and n is 1 to 4;

15 Another preferred embodiment is a compound of Formula

I



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wherein R is aryl, aryl lower alkyl, heterocyclic or
heterocyclic lower alkyl and R is unsubstituted or is
substituted with at least one electron withdrawing group, or
electron donating group;

25

R₁ is hydrogen or lower alkyl, unsubstituted or
substituted with an electron donating group or an electron
withdrawing group and

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R₂ and R₃ are independently hydrogen, lower alkyl,
lower alkenyl, lower alkynyl, aryl lower alkyl, aryl,
heterocyclic, heterocyclic lower alkyl, or Z-Y wherein R₂ and
R₃ may be unsubstituted or substituted with at least one

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12

1 electron withdrawing group or electron donating group;

Z is O, S, S(O)_a, NR₄, PR₄ or a chemical bond;

5 Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, or halo and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is NR₄NR₅R₇, NR₄OR₅, ONR₄R₇, OPR₄R₅, PR₄OR₅, SNR₄R₇, NR₄SR₇, SPR₄R₅ or PR₄SR₇, NR₄PR₅R₆ or

10 PR₄NR₅R₇, NR₄_{||}CR₅, SCR₅, NR₄_{||}COR₅, SC-OR₅

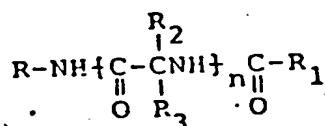
T180X
15 R₄, R₅ and R₆ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R₄, R₅ and R₆ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

20 R₇ is R₆ or COOR₈ or COR₈, R₈ is hydrogen or lower alkyl, or aryl lower alkyl, wherein the aryl or lower alkyl groups may be unsubstituted or substituted with an electron withdrawing or electron donating group,

n is 1-4 and

a is 1-3.

Another class of preferred compounds of the Formula I have the formula



30

35

18

1 wherein R is aryl, aryl lower alkyl, heterocyclic or heterocyclic alkyl which is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;

5 R_1 is hydrogen or lower alkyl which is unsubstituted or substituted with at least one electron withdrawing group or one electron donating group,

10 R_2 and R_3 are independently hydrogen, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, Z-Y or a heterocyclic group which may be unsubstituted or substituted with at least one electron withdrawing or one electron donating group, with the proviso that R^2 and R^3 cannot both be hydrogen;

Z is O, S, NR_4 , PR_4 or a chemical bond;

15 Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl or halo, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond; or

20 ZY taken together is $NR_4NR_5R_6$, NR_4OR_5 , ONR_4R_5 , OPR_4R_5 , PR_4OR_5 , SNR_4R_5 , NR_4SR_5 , SPR_4R_5 , or PR_4SR_5 , $NR_4PR_5R_6$ or $PR_4NR_5R_6$.

25 R_4 , R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

n is 1-4.

Of this preferred group, it is especially preferred that n is 1.

30 The preferred compounds are those in which R is aryl, aryl lower alkyl, heterocyclic, or heterocyclic lower alkyl, R_1 is hydrogen or lower alkyl, R_2 and R_3 are independently hydrogen, heterocyclic, lower alkyl, aryl, lower alkoxy, lower alkenyl, amino, hydroxylamino, lower alkoxy amino, N-lower

1 alkyl hydroxyamino, N-lower alkyl-o-lower alkyl hydroxyamino,
aralkoxy carbonyl hydrazino or alkylmercapto and n is 1.

5 In another preferred embodiment, n is 1, R and R₁ are
as defined hereinabove and one of R₂ and R₃ is hydrogen and the
other is heterocyclic, heterocyclic lower alkyl, aryl
N-hydroxylamino, lower alkoxyamino, N-lower alkylhydroxylamino,
N-lower alkyl-O-lower alkylhydroxyamino.

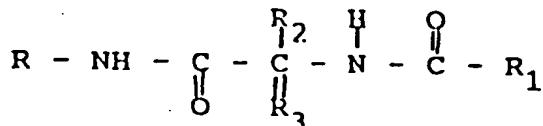
10 Another preferred embodiment is wherein n is 1, R and
R₁ are as defined hereinabove, one of R₂ and R₃ is as defined
hereinabove or the other is heterocyclic, heterocyclic lower
alkyl, lower alkyl heterocyclic, aryl, N-hydroxylamino, lower
alkoxy amino, N-lower alkyl hydroxylamino, N-lower
alkyl-o-lower alkyl hydroxylamino, lower alkoxy, dialkyl lower
amino, lower alkylamino, aryl lower alkyloxy hydrazino, or
lower alkylmercapto.

15 The various combination and permutations of the
Markush groups of R₁, R₂, R₃ R and n described herein are
contemplated to be within the scope of the present invention.
Moreover, the present invention also encompasses compounds and
compositions which contain one or more elements of each of the
20 Markush groupings in R₁, R₂, R₃, n and R and the various
combinations thereof. Thus, for example, the present invention
contemplates that R₁ may be one or more of the substituents
listed hereinabove in combination with any and all of the
substituents of R₂, R₃ and R with respect to each value of n.

25 The compounds of the present invention may contain
one (1) or more asymmetric carbons and may exist in racemic and
optically active forms. The configuration around each
asymmetric carbon can be in either the D or L form. (It is
well known in the art that the configuration around a chiral
30 carbon atoms can also be described as R or S in the
Cahn-Prelog-Ingold nomenclature system). All of the various
configurations around each asymmetric carbon, including the

1 various enantiomers and diastereomers as well as racemic mixtures and mixtures of enantiomers, diastereomers or both are contemplated by the present invention.

5 In the principal chain, there exists asymmetry at the carbon atoms to which the groups R_2 and R_3 are attached as substituted. When n is 1, the compounds of the present invention is of the formula



10 wherein R , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , Z and Y are as defined previously. As used herein, the term configuration shall refer to the configuration around the carbon atom to which R_2 and R_3 are attached, even though other chiral centers may be present in the molecule. Therefore, when referring to a particular configuration, such as D or L, it is to be understood to mean the stereoisomer, including all possible enantiomers and diastereomers. The compounds of the present invention are directed to all of the optical isomers, i.e., the compounds of the present invention are either the L-stereoisomer or the D-stereoisomer. These stereoisomers may be found in mixtures of the L and D stereoisomer, e.g., racemic mixtures. The D stereoisomer is preferred.

15 Depending upon the substituents, the present compounds may form addition salts as well. All of these forms are contemplated to be within the scope of this invention including mixtures of the stereoisomeric forms.

20 The following three schemes of preparation are generally exemplary of the process which can be employed for the preparation of the present complex. Although the compounds in the schemes hereinabove contain only the $\text{C}(=\text{O})\text{N}-$ moiety, it is

25 just as applicable to compounds of

30 Formula I wherein either A or Q is sulfur or both A or Q are sulfur.

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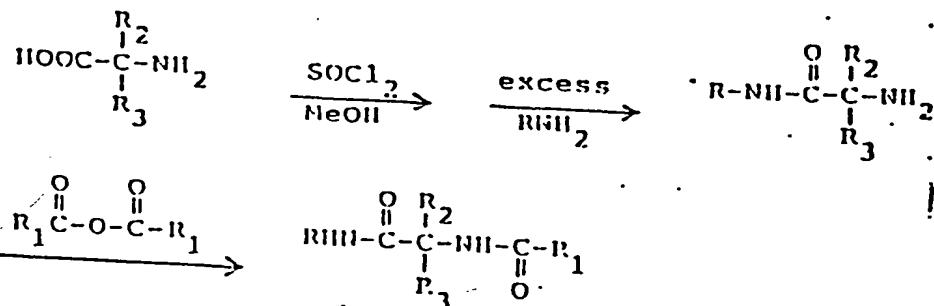
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T220X

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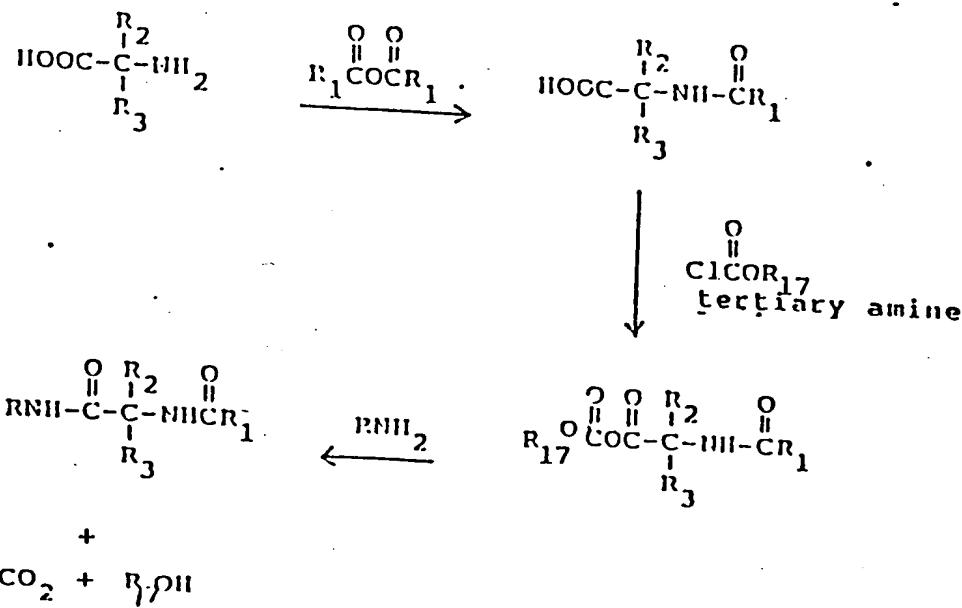
Scheme I



T221X

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Scheme II



30 35 wherein

R_{17} = lower alkyl, aryl, aryl lower alkyl,

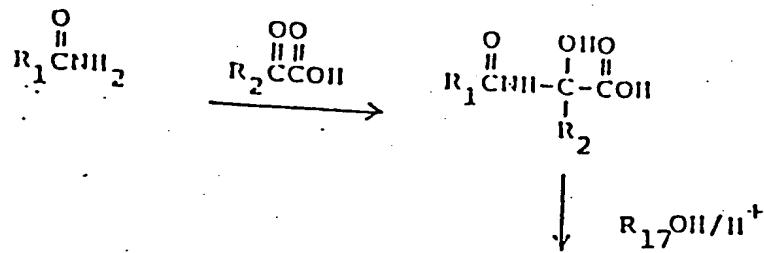
N
N

1

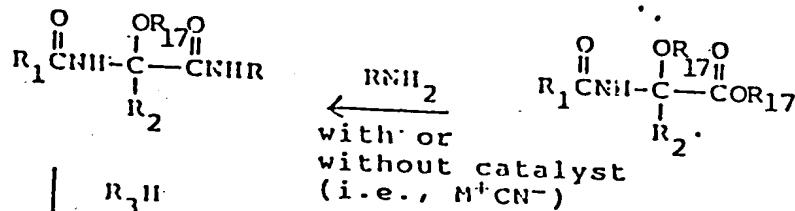
T23OK

Scheme III

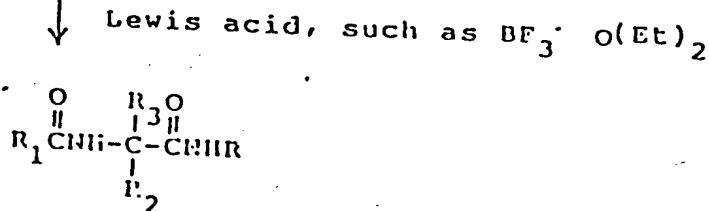
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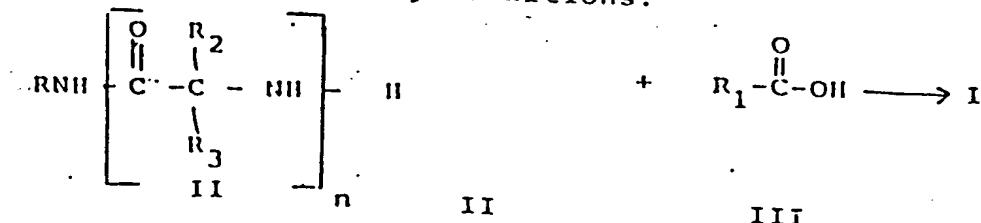


20

wherein R_3 = aryl, heteroaromatic and R_{17} is as defined hereinabove.

25

More specifically, these compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. For instance, compounds of Formula I can be prepared by reacting amines of Formula II with an acylating derivative of a carboxylic acid of Formula III under amide forming conditions:



35

wherein R , R_1 , R_2 , R_3 and n are as defined hereinabove and $n = 1$.

23

1 The amide forming conditions referred to herein
involve the use of known derivatives of the described acids,
such as the acyl halides, (e.g., $\text{R}_1\text{C}(=\text{O})\text{X}$,

5 wherein X is Cl, Br and the like), anhydrides

10 (e.g., $\text{R}_1\text{C}(=\text{O})\text{O}\text{C}(\text{R}_1)$), mixed anhydrides, lower alkyl esters,
carbodiimides, carbonyldiimidazoles, and the like. It is
preferred that the acylating derivative used is the

15 anhydride, $\text{R}_1\text{C}(=\text{O})\text{O}\text{C}(\text{R}_1)$. When alkyl esters are employed, amide
bond formation can be catalyzed by metal cyanides such as
sodium or potassium cyanides.

20 Another exemplary procedure for preparing compounds
wherein at least one of R_2 and R_3 is aromatic or heteroaromatic
is depicted in Scheme IV.

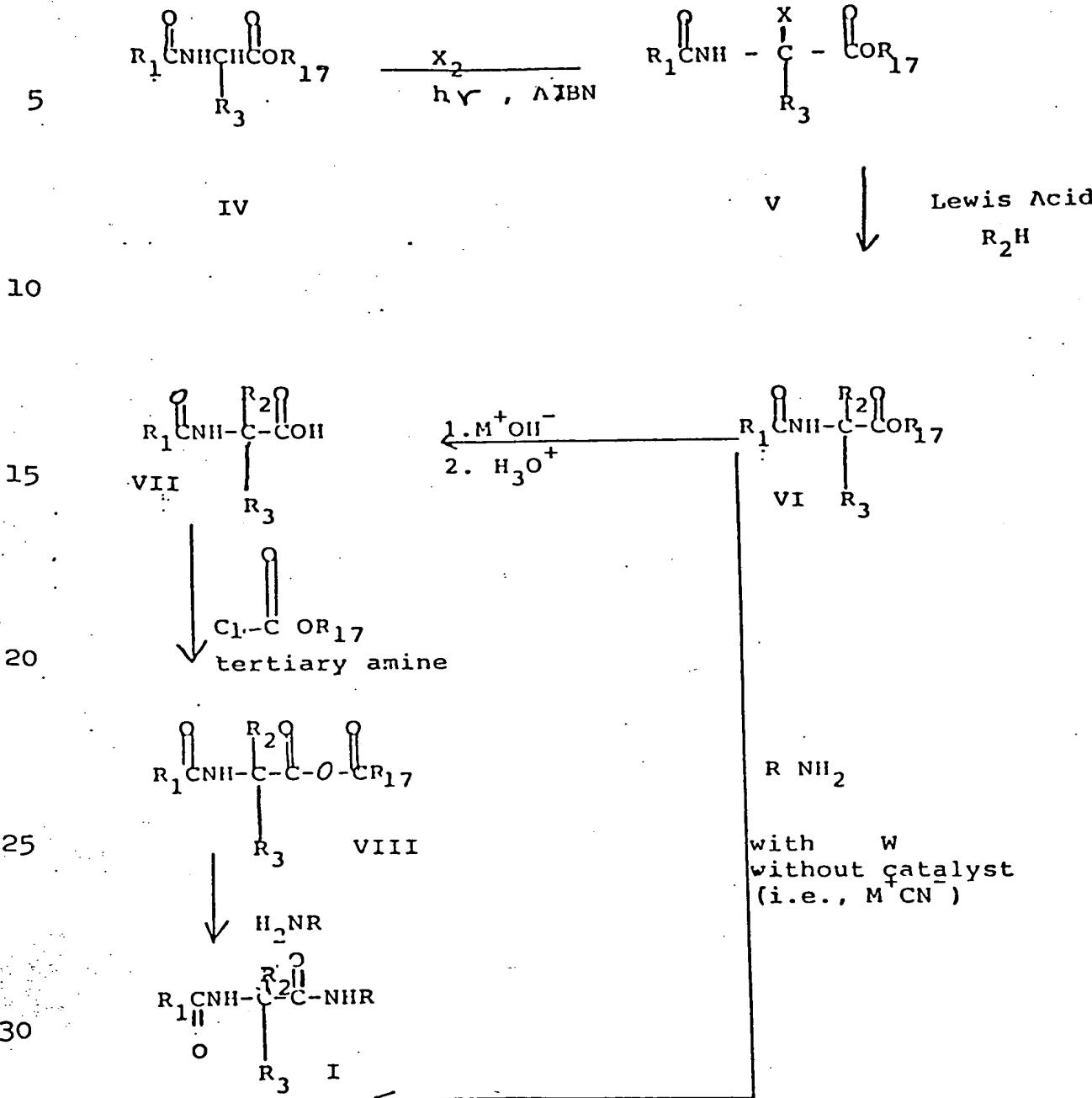
25 The ester (IV) is reacted with halogen and
ultraviolet light in the presence of a catalyst, e.g., AIBN, to
form the halo derivative (V). (V) is reacted in the presence
of a Lewis acid, such as zinc chloride, with an aromatic or
heteroaromatic compound to form the compound (VI). (VI) in
turn is hydrolyzed and then reacted with alkylhaloformate, such
as alkylchloroformate in the presence of a tertiary amine to
generate the mixed N-acyl amino acid carbonic ester anhydride
(VIII). This intermediate is reacted with an amine under amide
forming conditions to give the compound of Formula I.

30 Alternatively, (VI) can be reacted directly with an amine
(RNH_2) optionally in the presence of a metal catalyst, such as
metal cyanides, e.g., potassium or sodium cyanide, under amide
forming conditions to form a compound of Formula I.

35 Alternatively, compound VIII can be prepared by an independent
method and converted to VI which is then reacted with an amine,
with or without catalyst to form the compound of Formula I.

-24-

Scheme IV



X = halogen (i.e., Cl, Br)

R₁⁷=lower alkyl, aryl, arly lower alkyl

M⁺=metal cation (i.e., Na⁺, K⁺)

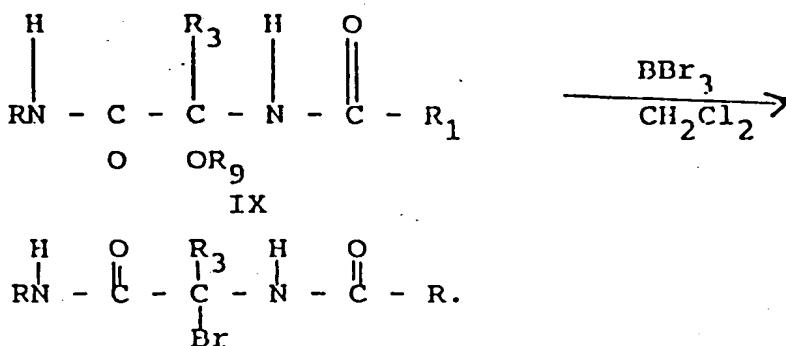
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Two additional synthetic routes may be employed for the preparation of compounds wherein R_2 or R_3 is Z-Y as defined hereinabove. In one scheme, for the preparation of these complexes, a substitution reaction is used:

5

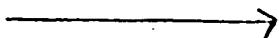
Scheme V

10



15

excess HR_2 or MR_2
THF (-78°C)



or

compound of Formula I,

20

- 1) Et_3N
- 2) HR_2
THF (-78°C)

25

In the above scheme, R_9 is lower alkyl, R_2 is Z-Y and Z, Y, R, R_3 and R_1 are as defined hereinabove.

30

The ether functionality on IX can be cleaved by treatment with Lewis acids, such as BBr_3 in an inert solvent such as methylene chloride to form the corresponding halo (bromo) derivative. Addition of either an excess of the H-R_2 or MR_2 or the sequential addition of triethylamine and H-R_2 to a THF mixture containing the halo derivative furnishes the desired product. For example, in the case wherein the compound of Formula IX is 2-acetamido-N-benzyl-2-ethoxy acetamide, its treatment with BBr_3 in CH_2Cl_2 led to the

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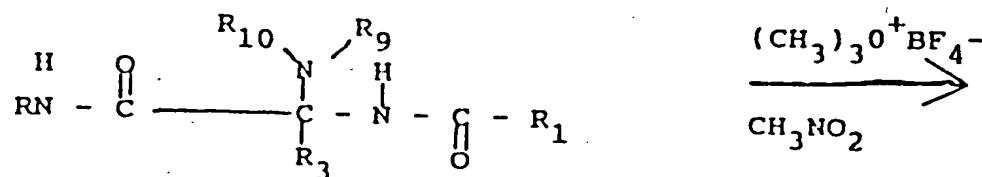
1 formation of the α -bromo derivative, 2-acetamido-N-benzyl-2-bromoacetamide. Addition of an excess of HR_2 or the sequential addition of HR_2 to a THF mixture containing the bromo adduct furnishes the desired product.

5 In another procedure, the product wherein R_2 or R_3 is Z-Y can also be prepared by substitution reaction on a quaternary ammonium derivative of the compound of Formula I as outlined below

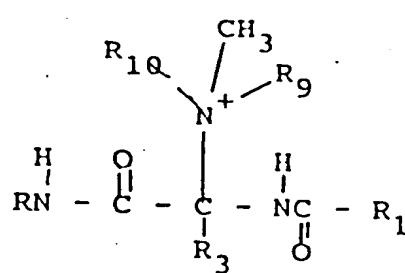
Scheme VI

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T270X

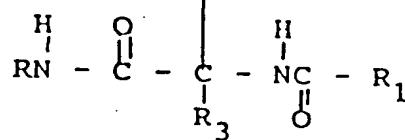


15



X

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In Scheme VI, R , R_1 , R_3 and R are as defined hereinabove, R_2 is Z-Y and R_9 and R_{10} are independently lower alkyl. In Scheme VI, methylation of compound X with a methylation reagent, such as trimethyloxonium tetrafluoroborate provided the corresponding ammonium derivative. Subsequent treatment of the ammonium salt with HR_2 furnishes the desired product. For example, methylation of

35

~X~

1 2-acetamido-N-benzyl-2-(N,N-dimethylamino) acetamide with
trimethyloxonium tetrafluoroborate in nitromethane furnished
the quaternary ammonium derivative,
2-acetamido-N-benzyl-(N,N,N-trimethylammonium) acetamide
5 tetrafluoroborate in high yields. Subsequent treatment of the
salt with the HR_2 reagent in the methanol leads to the
production of the desired product.

10 As in any organic reaction, solvents can be employed
such as methanol, ethanol, propanol, acetone, tetrahydrofuran,
dioxane, dimethylformamide, dichloromethane, chloroform, and
the like. The reaction is normally effected at or near room
temperature, although temperatures from 0°C up to the reflux
temperature of the reaction mixture can be employed.

15 As a further convenience, the amide forming reaction
can be effected in the presence of a base, such as tertiary
organic amine, e.g., triethylamine, pyridine,
4-methylmorpholine, picolines and the like, particularly where
hydrogen halide is formed by the amide forming reaction, e.g.,
the reaction acyl halide and the amine of Formula II. Of
course, in those reactions where hydrogen halide is produced,
20 any of the commonly used hydrogen halide acceptors can also be
used.

25 The exact mineral acid or Lewis acid employed in the
reaction will vary depending on the given transformation, the
temperature required for the conversion and the sensitivity of
the reagent toward the acid in the reaction employed.

Compounds of the present invention in which Q or
A is S are prepared from the corresponding compounds in
which Q or A is O by art recognized techniques. For
example, one reagent that can be used is Lawesson's reagent,
30 i.e., [2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-
diphosphetane-2-,4-disulfide]. This reagent is a known
reagent for the thiation of such compounds as ketones,
carboxamides, esters, lactones, lactams, imides, enamines,
35

1 and S-substituted thioesters. Thus, this reagent can be
used to transform compounds of Formula I wherein Q or A is

T290X
5 O to compounds wherein one or both of Q or A is S. The
number of $\text{C}=\text{C}$ groups in the final product is dependent upon
 $\begin{array}{c} \parallel \\ \text{S} \\ \backslash \end{array}$

T291X
the amount of reagent added and the number of $\text{C}=\text{C}$ groups
 $\begin{array}{c} \parallel \\ \text{O} \\ \backslash \end{array}$

10 present (i.e., the value of n) in the reactants having
Formula I. For example, if n is 1, and both Q and A are
oxygen, than the compounds of Formula I have two $\text{C}=\text{C}$ groups.
 $\begin{array}{c} \parallel \\ \text{O} \\ \backslash \end{array}$

T292X
T293X
Thus, if it is desired that both $\text{C}=\text{C}$ groups be transformed to
 $\begin{array}{c} \parallel \\ \text{O} \\ \backslash \end{array}$

T294X
 $\begin{array}{c} \parallel \\ \text{S} \\ \backslash \end{array}$ C then approximately equimolar amount or a slight excess of

20 is added to compounds of Formula I. On the other hand, if
only one $\text{C}=\text{C}$ group is desired in the final product,
 $\begin{array}{c} \parallel \\ \text{S} \\ \backslash \end{array}$

T295X
then approximately $\frac{1}{2}$ molar equivalent of Lawesson's reagent is used.

25 Furthermore, it is not necessary to add the
reagent at the last step of the synthesis; the reagent can
be added at any stage of the syntheses outlined in Schemes
I-VI hereinabove. As before, the amount of the reagent

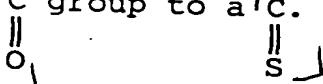
30 added depends upon the number of $\text{C}=\text{C}$ desired in the product, and the
 $\begin{array}{c} \parallel \\ \text{S} \\ \backslash \end{array}$

T296X
35 number of $\text{C}=\text{C}$ groups in the reactant.
 $\begin{array}{c} \parallel \\ \text{O} \\ \backslash \end{array}$

1 Regardless of which step in the synthesis the
reagent is added, the reagent and the compound of Formula I
having at least one C^{β} group or an intermediate thereof is



T300X
5 dissolved in an inert solvent, such as THF and heated at a
temperature effective to convert the C^{β} group to a C^{α} .



T301X, T302X
10 Temperatures ranging from room temperature to the reflux
temperature of the solvent can be used. In cases when
 $n = 1$, it is preferred that the reaction is heated to about
reflux if both Q and A are converted to S and that about
room temperature be used if one of Q or A is converted to
S.

15 The various substituents on the present new
compounds, e.g., as defined in R, R_1 , R_2 and R_3 can be present
in the starting compounds, added to any one of the
intermediates or added after formation of the final products by
the known methods of substitution or conversion reactions. For
20 example, the nitro groups can be added to the aromatic ring by
nitration and the nitro group converted to other groups, such
as amino by reduction, and halo by diazotization of the amino
group and replacement of the diazo group. Alkanoyl groups can
be substituted onto the aryl groups by Friedel-Crafts
25 acylation. The acyl groups can be then transformed to the
corresponding alkyl groups by various methods, including the
Woff-Kishner reduction and Clemmenson reduction. Amino groups
can be alkylated to form mono, dialkylamino and trialkylamino
groups; and mercapto and hydroxy groups can be alkylated to
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- 1 form corresponding thioethers or ethers, respectively. Primary
alcohols can be oxidized by oxidizing agents known in the art
to form carboxylic acids or aldehydes, and secondary alcohols
can be oxidized to form ketones. Thus, substitution or
5 alteration reactions can be employed to provide a variety of
substituents throughout the molecule of the starting material,
intermediates, or the final product.

In the above reactions, if the substituents
themselves are reactive, then the substituents can themselves
10 be protected according to the techniques known in the art. A
variety of protecting groups known in the art may be employed.
Examples of many of these possible groups may be found in
"Protective Groups in Organic Synthesis," by T.W. Greene, John
Wiley & Sons, 1981.

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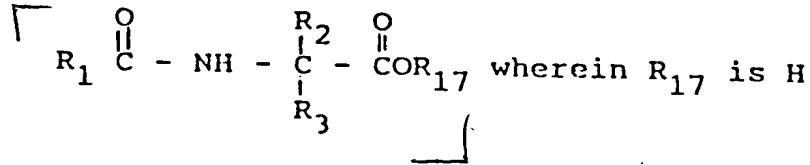
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1 Resulting mixtures of isomers can be separated in the
pure isomers by methods known to one skilled in the art, e.g.,
by fractional distillation, crystallization and/or
chromatography.

5 The present compounds obviously exist in
stereoisomeric forms and the products obtained thus can be
mixtures of the isomers, which can be resolved. Optically pure
functionalized amino acid derivatives can be prepared directly
from the corresponding pure chiral intermediate. Racemic
10 products can likewise be resolved into the optical antipodes,
for example, by separation of diastereomeric salts thereof,

15 e.g., by fractional crystallization, by selective enzymatic
hydrolysis, e.g., papain digestion, or by use of a chiral
stationary phase in chromatography (HPLC). For a discussion of
chiral stationary phases for HPLC, See, DeCamp, Chirality, 1,
2-6 (1989), which is incorporated herein by reference with the
same force and effect as if fully set forth herein.

20 For example, a racemic mixture of any of the
intermediate in any of the schemes, e.g.,



(which can be prepared according to the procedures of Schemes
1, 2, 3 or 4) is reacted with an optically active amine, RNH_2 ,
e.g., (R)(+)- α -methylbenzylamine to form a pair of
diastereomeric salts. Diastereomers can then be separated by
30 recognized techniques known in the art, such as fractional
recrystallization and the like.

1 In another method, a racemic mixture of final
products or intermediates can be resolved by using enzymatic
methods. Since enzymes are chiral molecules, it can be used to
separate the racemic modification, since it will preferentially
5 act on one of the compounds, without affecting the enantiomer.
For example, acylase, such as acylase I, can be used to
separate the racemic modification of an intermediate
 $D,L(\pm)\alpha$ -acetamido-2-furanacetic acid. It acts on the L
 $(\pm)\alpha$ -acetamido-2-furanacetic acid, but will not act on the D
10 enantiomer. In this way, the $D(-)\alpha$ -acetamido-2-furanacetic
acid can be isolated. The intermediate can then react with the
amine (RNH_2) under amide forming conditions as described
hereinabove to form teh compound of Formula I.

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1 The active ingredients of the therapeutic
compositions and the compounds of the present invention
exhibit excellent anticonvulsant activity when administered
in amounts ranging from about 10 mg to about 100 mg per
5 kilogram of body weight per day. A preferred dosage regimen
for optimum results would be from about 20 mg to about 50 mg
per kilogram of body weight per day, and such dosage units
are employed that a total of from about 1.0 gram to about 3.0
10 grams of the active compound for a subject of about 70 kg of
body weight are administered in a 24-hour period. This
dosage regimen may be adjusted to provide the optimum
therapeutic response and is preferably administered one to
three times a day in dosages of about 600 mg per
15 administration. For example, several divided doses may be
administered daily or the dose may be proportionally reduced
as indicated by the exigencies of the therapeutic situation.
A decided practical advantage is that the active compound may
be administered in an convenient manner such as by the oral,
intraveneous (where water soluble), intramuscular or
20 subcutaneous routes.

25 The active compound may be orally administered, for
example, with an inert diluent or with an assimilable edible
carrier, or it may be enclosed in hard or soft shell gelatin
capsule, or it may be compressed into tablets, or it may be
incorporated directly with the food of the diet. For oral
therapeutic administration, the active compound may be

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1 incorporated with excipients and used in the form of ingestible
5 tablets, buccal tablets, troches, capsules, elixirs,
suspensions, syrups, wafers, and the like. Such compositions
and preparations should contain at least 1% of active compound.
The percentage of the compositions and preparations may, of
course, be varied and may conveniently be between about 5 to
about 80% of the weight of the unit. The amount of active
10 compound in such therapeutically useful compositions is such
that a suitable dosage will be obtained. Preferred
compositions or preparations according to the present invention
are prepared so that an oral dosage unit form contains between
about 5 and 1000mg of active compound.

15 The tablets, troches, pills, capsules and the like
may also contain the following: A binder such as gum
tragacanth, acacia, corn starch or gelatin; excipients such as
dicalcium phosphate; a disintegrating agent such as corn
starch, potato starch, alginic acid and the like; a lubricant
such as magnesium stearate; and a sweetening agent such as
20 sucrose, lactose or saccharin may be added or a flavoring
agent such as peppermint, oil of wintergreen, or cherry
flavoring. When the dosage unit form is a capsule, it may
contain, in addition to materials of the above type, a liquid
carrier. Various other materials may be present as coatings or
25 to otherwise modify the physical form of the dosage unit. For
instance, tablets, pills, or capsules may be coated with
shellac, sugar or both. A syrup or elixir may contain the
active compound, sucrose as a sweetening agent, methyl and
propylparabens as preservatives, a dye and flavoring such as
30 cherry or orange flavor. Of course, any material used in
preparing any dosage unit form should be pharmaceutically pure
and substantially non-toxic in the amounts employed. In
addition, the active compound may be incorporated into

1 sustained-release preparations and formulations. For example,
sustained release dosage forms are contemplated wherein the
active ingredient is bound to an ion exchange resin which,
optionally, can be coated with a diffusion barrier coating to
5 modify the release properties of the resin.

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1 The active compound may also be administered
5 parenterally or intraperitoneally. Dispersions can also be
 prepared in glycerol, liquid polyethylene glycols, and
 mixtures thereof and in oils. Under ordinary conditions of
10 storage and use, these preparations contain a preservative to
 prevent the growth of microorganisms.

10 The pharmaceutical forms suitable for injectable
 use include sterile aqueous solutions (where water soluble)
 or dispersions and sterile powders for the extemporaneous
 preparation of sterile injectable solutions or dispersions.
15 In all cases the form must be sterile and must be fluid to
 the extent that easy syringability exists. It must be stable
 under the conditions of manufacture and storage and must be
 preserved against the contaminating action of microorganisms
20 such as bacteria and fungi. The carrier can be a solvent or
 dispersion medium containing, for example, water, ethanol,
 polyol (for example, glycerol, propylene glycol, and liquid
 polyethylene glycol, and the like), suitable mixtures
 thereof, and vegetable oils. The proper fluidity can be
25 maintained, for example, by the use of a coating such as
 lecithin; by the maintenance of the required particle size in
 the case of dispersion and by the use of surfactants. The
 prevention of the action of microorganisms can be brought
 about by various antibacterial and antifungal agents, for
 example, parabens, chlorobutanol, phenol, sorbic acid,
 thimerosal, and the like. In many cases, it will be
 preferable to include isotonic agents, for example, sugars or
 sodium chloride. Prolonged absorption of the injectable
 compositions can be brought about by the use in the
 compositions of agents delaying absorption, for example,
30 aluminum monostearate and gelatin.

1 Sterile injectable solutions are prepared by
incorporating the active compound in the required amount in
the appropriate solvent with various of the other ingredients
enumerated above, as required, followed by filtered
5 sterilization. Generally, dispersions are prepared by
incorporating the various sterilized active ingredient into a
sterile vehicle which contains the basic dispersion medium
and the required other ingredients from those enumerated
above. In the case of sterile powders for the preparation of
10 sterile injectable solutions, the preferred methods of
preparation are vacuum drying and the freeze-drying technique
which yield a powder of the active ingredient plus any
additional desired ingredient from previously sterile-
filtered solution thereof.

15 As used herein, "pharmaceutically acceptable
carrier" includes any and all solvents, dispersion media,
coatings, antibacterial and antifungal agents, isotonic and
absorption delaying agents, and the like. The use of such
media and agents for pharmaceutical active substances is well
known in the art. Except insofar as any conventional media
20 or agent is incompatible with the active ingredient, its use
in the therapeutic compositions is contemplated.
Supplementary active ingredients can also be incorporated
into the compositions.

25 It is especially advantageous to formulate
parenteral compositions in dosage unit form for ease of
administration and uniformity of dosage. Dosage unit form as
used herein refers to physically discrete units suited as
unitary dosages for the mammalian subjects to be treated;
each unit containing a predetermined quantity of active
30 material calculated to produce the desired therapeutic effect
in association with the required pharmaceutical carrier. The

1 specification for the novel dosage unit forms of the
invention are dictated by and directly dependent on (a) the
unique characteristics of the active material and the
particular therapeutic effect to be achieved, and (b) the
5 limitations inherent in the art of compounding such an active
material for the treatment of disease in living subjects
having a diseased condition in which bodily health is
impaired as herein disclosed in detail.

The principal active ingredient is compounded for
10 convenient and effective administration in effective amounts
with a suitable pharmaceutically acceptable carrier in dosage
unit form as hereinbefore disclosed. A unit dosage form can,
for example, contain the principal active compound in amounts
ranging from about 5 to about 1000 mg, with from about 250 to
15 about 750 mg being preferred. Expressed in proportions, the
active compound is generally present in from about 10 to
about 750 mg/ml of carrier. In the case of compositions
containing supplementary active ingredients, the dosages are
determined by reference to the usual dose and manner of
20 administration of the said ingredients.

The compounds of the present invention
may be administered in combination with other anti-convulsant
agents, such as phenytoin, phenobarbitol, mephenytoin,
and phenacemide, and the like. This combination
25 is likely to exhibit synergistic effects.

. For a better understanding of the present invention
together with other and further objects, reference is made to
the following description and examples.

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1 General Methods. Melting points were
determined with a Thomas-Hoover melting point apparatus
and are uncorrected. Infrared spectra (IR) were run on
a Beckman IR-4250 and Perkin-Elmer 1330 and 283
spectrophotometers and calibrated against the 1601-cm⁻¹
band of polystyrene. Absorption values are expressed in
wavenumbers (cm⁻¹). Proton nuclear magnetic resonance
(¹H NMR) spectra were recorded on Varian Associates
Models T-60 and FT-80A, General Electric QE 300, and
Nicolet NT-300 NMR spectrometers. Carbon nuclear
magnetic resonance (¹³C NMR) spectra were run on a
Varian Associates Models FT-80A General Electric QE 300
and Nicolet NT-300 instrument. Chemical shifts are in
parts per million (δ values) relative to Me₄Si, and
coupling constants (J values) are in hertz. Mass
spectral data were obtained at an ionizing voltage of 70
ev on a Hewlett-Packard 5930 gas chromatograph-mass
spectrometer and a Bell-Howell 21-491 spectrometer as
well as at the Eli Lilly Laboratories on a Varian
MAT-CH-5 spectrometer. High-resolution (EI mode) mass
spectra were performed by Drs. James Hudson and John
Chinn at the Department of Chemistry, University of
Texas at Austin, on a CEC21-110B double-focusing
magnetic-sector spectrometer at 70ev. Elemental
analyses were obtained at Spang Microanalytical
Laboratories, Eagle Harbor, MI and at the Eli Lilly
Research Laboratories.

20 The solvents and reactants were of the best
commercial grade available and were used without further
purification unless noted. All anhydrous reactions were
run under nitrogen, and all glassware was dried before
use. In particular, acetonitrile and triethylamine were
distilled from CaH₂, while dichloromethane was distilled
from P₂O₅. Acetic anhydride, benzaldehyde and ethyl
chloroformate were fractionally distilled.

1 Preparation of N-Acetyl-D- and L-amino acid-N-benzylamides.

General Procedure. The D- or L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane. The following examples 1-7 were prepared according to this procedure.

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EXAMPLE 1

Preparation of N-Acetyl-D,L-alanine-N'-benzylamide.

Acetic anhydride (2.20 g, 0.022 mol) was slowly
5 added to a methylene chloride solution (30 mL) of
D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to
stir at room temperature (3 h). The mixture was then succes-
sively washed with H₂O (15 mL), 1% aqueous NaOH (15 mL) and
H₂O (15 mL), dried (Na₂SO₄) and concentrated in vacuo.
10 The residue was recrystallized from CH₂Cl₂.
Yield: 2.50 g (54%).

mp 139-141°C.

¹H NMR (DMSO-d₆): δ 1.22 (d, J = 7.1 Hz, 3H), 1.84 (s, 3H),
4.04-4.50 (m, 3H), 7.26 (s, 5H), 8.11 (br d, J = 7.3 Hz,
1H), 8.42 (br t, J = 6 Hz, 1H).

15 ¹³C NMR (DMSO-d₆): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9,
128.1, 139.4, 168.9, 172.4 ppm.

IR (CHCl₃) 3440, 3300, 3005, 1660, 1515 cm⁻¹.

Mass spectrum (CI mode), m/e: 221 (P+1); mol wt 220.1208
20 (Calculated for C₁₂H₁₆N₂O₂, 220.1212).

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EXAMPLE 2

N-Acetyl-D-alanine-N'-benzylamide.

Yield: 1.36 g (56%).

mp 139-141°C.

$[\alpha]_D^{23} = +36.2$ (c 2.5, MeOH).

^1H NMR (80 MHz, DMSO-d₆): δ 1.25 (d, J = 7.1 Hz, 3H), 1.86 (s, 3H), 4.10-4.50 (m, 1H), 4.30 (d, J = 6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d, J = 7.3 Hz, 1H), 8.40 (t, J = 6.0 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d₆): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695 cm⁻¹.

Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

Elemental analysis

Calculated for C₁₂H₁₆N₂O₂ 65.42% C; 7.34% H; 12.72% N.

Found 65.31% C; 7.28% H; 12.63% N.

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EXAMPLE 3

N-Acetyl-L-alanine-N'-benzylamide.

Yield: 1.11 g (46%).

mp 139-142°C.

$[\alpha]_D^{23} = -35.3$ (c 2.5, MeOH).

^1H NMR (80 MHz, DMSO-d₆): δ 1.23 (d, J = 7.2 Hz, 3H), 1.86 (s, 3H), 4.26-4.35 (m, 1H), 4.29 (d, J = 5.8 Hz, 2H), 7.22-7.33 (s, 5H), 8.10 (d, J = 7.4 Hz, 1H), 8.42 (t, J = 5.8 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d₆): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C), 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695 cm⁻¹.

Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

Elemental analysis

Calculated for C₁₂H₁₆N₂O₂ 65.42% C; 7.34% H; 12.72% N.
Found 65.58% C; 7.32% H; 12.43% N.

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1 EXAMPLE 4

5 Preparation of N-Acetyl-D,L-phenylglycine-N'-methylamide.

Acetic anhydride (2.90 g, 28 mmol) was added dropwise to D,L-phenylglycine-N-methylamide (3.4 g, 20 mmol) and allowed to stir at room temperature (1.5 h). During this time, a copious white precipitate formed. This material was collected by filtration, dried in vacuo and recrystallized from absolute alcohol.

10 Yield: 2.00 g (49%).

mp 232-235°C (dec).

15 ^1H NMR (DMSO-d₆): δ 1.89 (s, 3H), 2.58 (d, J = 4.6 Hz, 3H), 5.42 (d, J = 8.1 Hz, 1H), 7.35 (s, 5H), 8.18 (br q, J = 4.2 Hz, 1H), 8.47 (d, J = 8.1 Hz, 1H).

20 ^{13}C NMR (DMSO-d₆): 22.4, 25.5, 56.3, 127.1, 127.3, 128.1, 139.0, 168.9, 170.3 ppm.

IR (KBr): 3310, 1645 cm⁻¹.

Mass spectrum (CI mode), m/e: 207 (P+1).

Elemental analysis

25 Calculated for C₁₁H₁₄N₂O₂ 64.06% C; 6.86% H; 13.58% N.

Found 63.79% C; 6.66% H; 13.27% N.

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EXAMPLE 5

Preparation of N-Acetylglycine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 1.84 g (81%).

mp 140-142°C.

^1H NMR (DMSO-d₆): δ 1.88 (s, 3H), 3.74 (d, $J = 5.3$ Hz, 2H), 4.30 (d, $J = 5.1$ Hz, 2H), 7.27 (s, 5H), 8.37 (br s, 1H), 8.75 (br s, 1H).

^{13}C NMR (DMSO-d₆): 22.5, 42.0, 42.5, 126.6, 127.1 (2C), 128.1 (2C), 139.3, 169.0, 169.6 ppm.

IR (KBr): 3060, 1655, 1640, 1560, 1545, 1450, 1300, 740, 710 cm^{-1} .

Mass spectrum, m/e (relative intensity): 206 (3), 147 (12), 106 (100), 91 (75), 73 (50).

Elemental analysis

Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ 64.05% C; 6.86% H; 13.58% N.

Found 64.03% C; 6.79% H; 13.61% N.

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EXAMPLE 6

Preparation of N-Acetyl-D,L-valine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.35 g (86%).

mp 192-193°C.

^1H NMR (DMSO-d₆): δ 0.83 (d, J = 6.7 Hz, 6H), 1.87 (s, 3H), 1.73-2.09 (m, 1H), 4.11 (d, J = 8.8 Hz, 1H), 4.27 (d, J = 5.8 Hz, 2H), 7.26 (s, 5H), 7.89 (d, J = 8.8 Hz, 1H), 8.84 (t, J = 5.8 Hz, 1H).

^{13}C NMR (DMSO-d₆): 18.1, 19.2, 22.4, 30.2, 41.9, 57.8, 126.6, 127.1 (2C), 128.1 (2C), 139.4, 169.2, 171.1 ppm.

IR (KBr): 1625, 1540, 1535, 1450, 1380, 1290, 750, 695 cm⁻¹. Mass spectrum, m/e (relative intensity): 142 (16), 114 (43), 106 (29), 91 (57), 72 (100).

Elemental analysis

Calculated for C₁₄H₂₀N₂O₂ 67.70% C; 8.13% H; 11.28% N.

Found 67.58% C; 8.05% H; 11.10% N.

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EXAMPLE 7

Preparation of N-Acetyl-D,L-phenylglycine-N-benzylamide.

5 The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

10 Yield: 2.05 g (66%).

mp 202-203°C.

15 ^1H NMR (DMSO-d₆): δ 1.91 (s, 3H), 4.27 (d, J = 5.6 Hz, 2H), 5.50 (d, J = 7.9 Hz, 1H), 7.21 (s, 5H), 7.36 (s, 5H), 8.38-8.86 (m, 2H).

20 ^{13}C NMR (DMSO-d₆): 22.3, 42.0, 56.3, 126.6 (2C), 127.0, 127.1 (2C), 127.4 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 169.9 ppm.

25 IR (KBr): 3020, 1635, 1580, 1540, 1450, 1265, 745, 690 cm⁻¹. Mass spectrum, m/e (relative intensity): 283 (20), 264 (21), 149 (100), 131 (20), 118 (34), 106 (92), 91 (70), 79 (56), 77 (54), 65 (45), 51 (37).

Elemental analysis

Calculated for C₁₇H₁₈N₂O₂: 72.31% C; 6.44% H; 9.92% N.

Found: 72.49% C; 6.47% H; 9.89% N.

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1 Preparation of N-Acetyl-D- and L-phenylglycine-N-benzylamide.

5 General Procedure. The chiral Boc-protected phenylglycine-N-benzylamide was dissolved in trifluoroacetic acid (0.04 M) and was stirred at room temperature (30 min), during which time gas evolved. The solution was concentrated in vacuo and the residue was redissolved in enough methanol to form a solution of 0.2 M. Methanesulfonic acid (1 equiv) was added dropwise and stirred for 5 min. After concentrating the solution in vacuo, the residue was repeatedly dissolved in methanol and the solvent was removed (3 times). The residue was then dried under vacuum (18 h), leaving a yellow oil.

10 Without further purification, the phenylglycine-N-benzylamide methanesulfonate was dissolved in tetrahydrofuran (0.2 M) and then was cooled in an ice bath. Triethylamine (2 equiv) was added dropwise, followed by acetyl chloride (1 equiv). The ice bath was removed and stirring was continued at room temperature (18 h). The solution was concentrated in vacuo and the residue was recrystallized from 1:1 95% ethanol/water. Examples 8 and 9 were prepared according to this procedure.

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EXAMPLE 8

N-Acetyl-D-phenylglycine-N-benzylamide.

The reaction was run on an 11.9 mmol scale.

Yield: 2.97 g (88%).

mp 219-221°C.

$[\alpha]_D = -103.0$ (c 1%, EtOH).

^1H NMR (DMSO-d₆): δ 1.91 (s, 3H), 4.27 (d, $J = 5.5$ Hz, 2H), 5.50 (d, $J = 7.8$ Hz, 1H), 7.14-7.44 (m, 10H), 8.56 (d, $J = 7.8$ Hz, 1H), 8.79 (t, $J = 5.5$ Hz, 1H).

^{13}C NMR (DMSO-d₆): 22.4, 42.0, 56.4, 126.7, 127.0 (2C), 127.2 (2C), 127.4, 127.9 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 170.0 ppm.

IR (KBr): 3260, 1620, 1525, 1450, 1370, 720, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 203 (2), 149 (94), 106 (100), 91 (32), 86 (43), 77 (14).

Elemental analysis

Calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ 72.32% C; 6.43% H; 9.92% N.

Found 72.04% C; 6.22% H; 9.78% N.

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EXAMPLE 9

N-Acetyl-L-phenylglycine-N-benzylamide.

Beginning with 16.1 mmol N-t-Boc-L-phenylglycine-
5 N-benzylamide.

Yield: 2.99 g (66%).

mp 221-222°C.

$[\alpha]_D = +105.1$ (c 1%, EtOH).

10 ^1H NMR (DMSO-d₆): δ 1.99 (s, 3H), 4.36 (d, J = 5.6 Hz, 2H),
5.60 (d, J = 8.0 Hz, 1H), 7.23-7.53 (m, 10H), 8.60 (d, J =
8.0 Hz, 1H), 8.83 (t, J = 5.6 Hz, 1H).

15 ^{13}C NMR (DMSO-d₆): 22.4, 42.1, 56.5, 126.8, 127.1 (2C),
127.3 (2C), 127.5, 128.2 (4C), 139.0, 139.1, 169.1,
170.1 ppm.

15 IR (KBr): 3295, 1630, 1530, 1450, 1395, 720, 695 cm⁻¹.
Mass spectrum, m/e (relative intensity): 223 (1), 203 (2),

149 (98), 106 (100), 91 (32), 86 (43), 77 (11).

Elemental analysis

Calculated for C₁₇H₁₈¹⁵O₂ 72.32% C; 6.43% H; 9.92% N.

20 Found 72.53% C; 6.49% H; 9.67% N.

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Preparation of N-Acetyl-D,L-alanine-N-(3-methoxy)benzylamide.

5 The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

10 Yield: 0.47 g (17%).

mp 112-115°C.

15 ^1H NMR (DMSO-d₆): δ 1.23 (d, J = 7.1 Hz, 3H), 1.85 (s, 3H), 3.73 (s, 3H), 3.99-4.48 (m, 1H), 4.25 (d, J = 6.1 Hz, 2H), 6.58-7.35 (m, 4H), 8.05 (d, J = 7.4 Hz, 1H), 8.35 (t, J = 6.0 Hz, 1H).

20 ^{13}C NMR (DMSO-d₆): 18.1, 22.5, 41.8, 48.3, 54.9, 112.2, 112.3, 119.0, 129.2, 141.0, 159.3, 169.0, 172.4 ppm.

IR (KBr): 3270, 3065, 1625, 1580, 1450, 1260, 1150, 1095, 900, 775, 700, 690 cm⁻¹.

25 Elemental analysis

Calculated for C₁₃H₁₈N₂O₃: 62.37% C; 7.26% H; 11.19% N.
Found 62.29% C; 7.13% H; 11.08% N.

1 EXAMPLE 11

Preparation of N-Trimethylacetyl-D,L-alanine-N-benzylamide.

5 D,L-Alanine-N-benzylamide (3.56 g, 20 mmol) was dissolved in dichloromethane (25 mL) and trimethylacetic anhydride (4.10 g, 4.46 mL, 22 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The solid residue was recrystallized from benzene/petroleum ether (30-60°C).

10 Yield: 2.07 g (40%).

mp 123-124°C.

15 ^1H NMR (DMSO-d₆): δ 1.12 (s, 9H), 1.27 (d, J = 7.1 Hz, 3H), 4.23-4.42 (m, 1H), 4.31 (d, J = 5.4 Hz, 2H), 7.23-7.30 (m, 5H), 7.38 (d, J = 7.4 Hz, 1H), 8.26 (t, J = 5.4 Hz, 1H).

20 ^{13}C NMR (DMSO-d₆): 18.1, 27.2 (3C), 37.9, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 172.5, 177.1 ppm.

25 IR (KBr): 3300, 1630, 1535 (br), 1455, 745, 695 cm⁻¹.

Mass spectrum, m/e (relative intensity): 262 (2), 203 (19), 156 (18), 128 (51), 106 (31), 91 (100), 77 (15), 65 (28).

Elemental analysis

Calculated for C₁₅H₂₂N₂O₂ 68.66% C; 8.47% H; 10.68% N.

Found 68.91% C; 8.14% H; 10.61% N.

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EXAMPLE 12

Preparation of N-Acetyl-D,L-methionine-N-benzylamide.

5 N-Acetyl-D,L-methionine (4.78 g, 25 mmol) was combined with acetonitrile (75 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (2.53 g, 3.48 mL, 25 mmol) was added dropwise, followed by ethyl chloroformate (2.71 g, 2.39 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (3.00 g, 3.06 mL, 28 mmol) in acetonitrile (5 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h).

10 The mixture was filtered and a white precipitate was collected and dried in vacuo and identified as the desired product (^1H NMR and ^{13}C NMR analyses). The filtrate was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride.

15 The latter filtrate containing tetrahydrofuran was concentrated in vacuo and the resulting residue was purified by flash column chromatography (ethyl acetate). A white solid ($R_f = 0.50$, ethyl acetate) was isolated and was identified as the desired product (^1H NMR and ^{13}C NMR analyses). The two solids identified as N-acetyl-D,L-methionine-N-benzylamide were combined and recrystallized from benzene/petroleum ether (30-60°C).

20 Yield: 2.98 g (43%).

25 mp 134-135°C.

30 ^1H NMR (DMSO- d_6): δ 1.69-1.94 (m, 2H), 1.87 (s, 3H), 2.02 (s, 3H), 2.29-2.59 (m, 2H), 4.10-4.53 (m, 1H), 4.29 (d, $J = 6.0$ Hz, 2H), 7.26 (s, 5H), 8.12 (d, $J = 8.5$ Hz, 1H), 8.47 (t, $J = 6.0$ Hz, 1H).

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1 ^{13}C NMR (DMSO-d₆): 14.6, 22.5, 29.7, 31.8, 42.0, 52.0,
126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.5, 171.4 ppm.

IR (KBr): 3280, 1630, 1545, 1460, 750, 700 cm⁻¹.

5 Mass spectrum, m/e (relative intensity): 280 (3), 206 (100),
164 (29), 146 (20), 106 (54), 91 (76), 77 (14), 65 (24).

Elemental analysis

Calculated for C₁₄H₂₀N₂O₂S 59.96% C; 7.20% H; 9.99% N.

Found 60.02% C; 7.14% H; 9.91% N.

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EXAMPLE 13

Preparation of N-Acetylalanine-N'-(3-fluoro)benzylamide.

N-Acetylalanine (3.28 g, 25 mmol) was combined with acetonitrile (100 mL) and the mixture was placed into an ice/salt bath at -5°C. Triethylamine (2.53 g, 3.5 mL, 25 mmol) was added dropwise followed by the addition of ethyl chloroformate (2.71 g, 2.40 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C for 20 minutes. 3-Fluorobenzylamine (3.58 g, 28 mmol) and acetonitrile (5 mL) was added dropwise and was stirred at -5°C for one hour and then at room temperature for 18 hours. The reaction became homogenous during this time interval.

The solution was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (100 mL) and cooled in the freezer for 3 hours resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo and identified as triethylammonium hydrochloride (3.51 g, mp 253-257°C). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from chloroform/diethyl ether. Yield: 3.22 g (54%).

mp 120-121°C.

¹H NMR (DMSO-d₆): δ 1.27 (d, J = 7.1 Hz, 3H), 1.90 (s, 3H), 4.23-4.41 (m, 1H), 4.33 (d, J = 6.1 Hz, 2H), 7.05-7.37 (m, 4H), 8.19 (d, J = 7.1 Hz, 1H), 8.53 (t, J = 6.1 Hz, 1H).

¹³C NMR (DMSO-d₆): 17.9, 22.4, 41.5, 48.5, 113.3 (d, J = 20.4 Hz), 113.5 (d, J = 21.7 Hz), 122.8, 130.1 (d, J = 7.9 Hz), 142.4 (d, J = 7.4 Hz), 162.3 (d, J = 243.6 Hz), 169.6, 172.8 ppm.

IR (KBr): 3280, 1645, 1545, 1450, 745, 680 cm⁻¹.

1 Mass spectrum, m/e (relative intensity): 238 (18), 151 (22),
124 (49), 114 (47), 109 (100), 87 (76), 72 (27).
Elemental analysis

5 Calculated 60.48% C; 6.36% H; 11.76% N.
 Found 60.55% C; 6.32% H; 11.71% N.

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EXAMPLE 14

Preparation of D,L- α -Acetamido-N-benzyl-3-thiopheneacetamide.

D,L- α -Acetamido-3-thiopheneacetic acid (2.99 g, 5 mmol) was combined with acetonitrile (60 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (1.51 g, 2.10 mL, 15 mmol) was added dropwise, followed by ethyl chloroformate (1.63 g, 1.43 mL, 15 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (1.77 g, 1.80 mL, 16.5 mmol) in acetonitrile (10 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h). The mixture was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride (^1H NMR analysis). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from 1:1 95% ethanol/water. Yield: 1.91 g (44%).

mp 198-199°C.

^1H NMR (DMSO- d_6): δ 1.91 (s, 3H), 4.29 (d, J = 5.2 Hz, 2H), 5.61 (d, J = 7.9 Hz, 1H), 7.15-7.50 (m, 3H), 8.55 (d, J = 7.9 Hz, 1H), 8.74 (t, J = 5.2 Hz, 1H).

^{13}C NMR (DMSO- d_6): 22.3, 42.0, 52.5, 122.4, 126.1, 126.7, 127.0 (3C), 128.2 (2C), 139.0, 139.2, 169.0, 169.8 ppm.

IR (KBr): 3460, 1675, 1570, 1400, 720, 695 cm^{-1} .

Mass spectrum, m/e (relative intensity): 288 (2), 245 (3), 30 155 (88), 112 (100), 91 (31), 85 (17), 65 (7).

Elemental analysis

Calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ 62.48% C; 5.59% H; 9.71% N.

Found 62.41% C; 5.47% H; 9.55% N.

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EXAMPLE 15

Preparation of D,L- α -Acetamido-N-benzyl-2-thiopheneacetamide

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (6.26 g, 25 mmol) was combined with dry ether (175 mL) and then boron trifluoride etherate (5.68 g, 5.0 mL, 40 mmol) was added dropwise, resulting in a homogeneous solution. After stirring a short time, a small amount of a yellow oil separated from the solution. Thiophene (8.41 g, 8.0 mL, 100 mmol) was then added dropwise via syringe and the reaction was stirred at room temperature (4 d). The mixture was cooled in an ice bath and cold aqueous saturated NaHCO₃ (200 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic washings and the original ether layer were combined, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography, using 94:6 chloroform/methanol as an eluant (R_f = 0.7 94:6 chloroform/methanol), and then recrystallized from benzene.

Yield: 2.67 g (37%).

mp 167-169°C.

¹H NMR (DMSO-d₆): δ 1.91 (s, 3H), 4.31 (d, J = 6.0 Hz, 2H), 5.74 (d, J = 7.9 Hz, 1H), 6.99-7.44 (m, 8H), 8.64 (d, J = 7.9 Hz, 1H), 8.85 (t, J = 6.0 Hz, 1H).

¹³C NMR (DMSO-d₆): 22.4, 42.3, 52.2, 125.6, 125.8, 126.6, 126.9, 127.3 (2C), 128.3 (2C), 139.0, 141.4, 169.2, 169.3 ppm.

Mass spectrum, m/e (relative intensity): 289 (2), 181 (6), 155 (100), 112 (100), 91 (100), 85 (34), 74 (24).

Elemental analysis

Calculated for C₁₅H₁₆N₂O₂S 62.48% C; 5.59% H; 9.71% N.

Found 62.64% C; 5.73% H; 9.61% N.

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1 EXAMPLE 16

Preparation of D,L- α -Acetamido-N-benzyl-2-furanacetamide.

N-Acetyl-D,L-2-(2-furyl)glycine (0.47 g, 2.56 mmol) was combined with acetonitrile (10 mL) and cooled to -5°C (ice/salt water bath). Triethylamine (0.26 g, 0.36 mL, 2.56 mmol) was then rapidly added and the mixture stirred at -5°C (3 min). Ethyl chloroformate (0.28 g, 0.25 mL, 2.56 mmol) was added dropwise between -4°C and -3°C, and the resulting suspension was stirred at -4°C (20 min), and then an acetonitrile solution (2 mL) of benzylamine (0.30 g, 0.31 mL, 2.82 mmol) was carefully added. During the addition of benzylamine the temperature of the solution did not go above 0°C. The mixture was stirred at -5°C (1 h) and at room temperature (18 h), and then concentrated in vacuo. The residue was then triturated with hot tetrahydrofuran (5 mL), cooled at -16°C (3 h), and the resulting white precipitate was filtered and identified as triethylamine hydrochloride (¹H NMR, 60 MHz, δ 1.00 (t, J = 7.5 Hz, CH₃), 2.82 (q, J = 7.5 Hz, CH₂), 3.83 (s, NH)). The filtrate was evaporated to dryness in vacuo and the resulting oil purified by flash chromatography (98:2 chloroform/methanol) to give 0.09 g (13%) of the desired product as a white solid: R_f 0.30 (98:2 chloroform/methanol).

mp 178-179°C.

¹H NMR (300 MHz, DMSO-d₆): δ 1.90 (s, CH₃), 4.31 (d, J = 6.0 Hz, CH₂), 5.58 (d, J = 8.1 Hz, CH), 6.27-6.33 (m, C₃'H), 6.40-6.44 (m, C₄'H), 7.20-7.36 (m, Ph), 7.60-7.64 (m, C₅'H), 8.57 (d, J = 8.1 Hz, NH), 8.73 (t, J = 6.0 Hz, NH).
¹³C NMR (300 MHz, DMSO-d₆): 22.35 (CH₃), 42.27 (CH₂), 50.95 (CH), 107.60 (C₃''), 110.55 (C₄''), 126.82 (2C₂'' or 2C₃'''), 127.08 (2C₂'' or 2C₃'''), 128.27 (C₄'''), 139.05 (C₁'''), 142.58 (C₅''), 151.16 (C₂''), 168.02 (CH₃CO), 169.30 (NHCO) ppm.

1 IR (KBr): 3230, 1625 (br), 1525 (br), 1375 (br), 1230, 1090,
890 cm⁻¹.

Mass spectrum, m/e (relative intensity): 273 (1), 139 (100),
96 (94), 91 (51), 65 (9).

5 Elemental analysis

Calculated for C₁₅H₁₆N₂O₃ Found 66.16% C; 5.83% H; 10.29% N.
65.92% C; 5.83% H; 10.15% N.

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EXAMPLE 17

Preparation of D,L- α -Acetamido-N-benzyl-2-pyrroleacetamide.

2-Acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether (60 mL), and then boron trifluoride etherate (1.82 g, 1.57 mL, 12.8 mmol) was added in one portion and the resulting solution was stirred (15 min). The pyrrole (2.14 g, 2.22 mL, 32 mmol) was then added in one portion and the solution was stirred at room temperature (48 h) during which time a precipitate formed. Hexanes (80 mL) were then added to the suspension, and the mixture was filtered and the brown semi-solid was triturated with 95:5 chloroform/methanol (30 mL) to furnish a green solid. This material was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.94 g (35%) of the desired product as a white solid: R_f 0.29 (96:4 chloroform/methanol).

mp 174-175°C.

^1H NMR (300 MHz, CD_3CN): δ 1.93 (s, CH_3), 4.35 (d, $J = 6.0$ Hz, CH_2), 5.42 (d, $J = 6.9$ Hz, CH), 6.00-6.18 (m, $\text{C}_3\text{-H}$, $\text{C}_4\text{-H}$), 6.68-6.72 (m, $\text{C}_5\text{-H}$), 7.04 (d, $J = 6.9$ Hz, NH), 7.17 (t, $J = 6.0$ Hz, NH), 7.10-7.47 (m, Ph), 9.10-9.80 (br s, NH).

^{13}C NMR (300 MHz, CD_3CN): 23.02 (CH_3), 43.83 (CH_2), 52.65 (CH), 107.57 (C_3), 108.85 (C_4), 119.33 (C_5), 127.96 (C_2), 128.01 (2C_2 or 2C_3), 128.09 (2C_2 or 2C_3), 129.49 (C_4), 140.01 (C_1), 170.94 (COCH_3), 171.21 (CONH) ppm.

IR (KBr): 3320, 1570 (br), 1470 (br), 1330, 1230, 950, 890, 860, 760, 710, 690, 655 cm^{-1} .

Mass spectrum, m/e (relative intensity): 171 (12), 228 (2), 213 (1), 180 (2), 164 (9), 137 (93), 108 (20), 95 (100), 91 (38), 82 (35), 68 (15).

High resolution mass spectral analysis

Calculated for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$ 271.13208.

35 Found 271.13144.

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EXAMPLE 18

Preparation of D,L-2-Acetamido-N-benzyl-2-ethoxyacetamide.

An ethanolic solution (420 mL) of ethyl 2-acetamido-2-ethoxyacetate (27.92 g, 147 mmol) and benzylamine (23.70 g, 24 mL, 221 mmol) was stirred at 40-45°C for 3 days. The reaction mixture was evaporated in vacuo and the residue recrystallized (1:3.5 tetrahydrofuran/hexanes (650 mL)) to yield 25.80 g (70%) of the desired product as beige crystals: R_f 0.59 (95:5 chloroform/methanol).
mp 153-155°C.

^1H NMR (300 MHz, CDCl_3): δ 1.20 ($t, J = 7.0$ Hz, CH_3), 2.07 (s, CH_3), 3.60-3.76 (m, CH_2CH_3), 4.40-4.54 (m, CH_2NH), 5.60 (d, $J = 8.7$ Hz, CH), 6.63 (d, $J = 8.7$ Hz, NH), 7.00 (br s, NH), 7.26-7.36 (m, Ph).

^{13}C NMR (300 MHz, CDCl_3): 15.06 (CH_3CH_2), 23.25 (CH_3CO), 43.60 (CH_2NH), 64.51 (CH_2CH_3), 77.43 (CH), 127.69 ($2\text{C}_2^{..}$ or $2\text{C}_3^{..}, \text{C}_4^{..}$), 128.79 ($2\text{C}_2^{..}$ or $2\text{C}_3^{..}$), 137.57 ($\text{C}_1^{..}$), 168.13 (COCH_3), 171.29 (CONH) ppm.

IR (KBr): 3260, 1630 (br), 1550 (sh), 1505 (br), 1380, 1360, 1230, 1115, 1060, 1015, 890, 745, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 251 (4), 163 (9), 116 (98), 106 (34), 91 (98), 74 (100).

Elemental analysis

Calculated for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$ 62.38% C; 7.25% H; 11.19% N.
Found 62.49% C; 7.27% H; 11.24% N.

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EXAMPLE 19

Preparation of D,L-2-Acetamido-N-benzyl-2-methoxyacetamide.

To a methanolic solution (180 mL) of methyl 2-acetamido-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50°C (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2x) to give 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95:5 chloroform/methanol). mp 145-146°C.

^1H NMR (300 MHz, CDCl_3): δ 2.06 (s, CH_3CO), 3.37 (s, CH_3O), 4.40-4.35 (m, CH_2), 5.52 (d, $J = 8.7$ Hz, CH), 7.12 (d, $J = 8.7$ Hz, NH), 7.20-7.40 (m, Ph, NH).

^{13}C NMR (300 MHz, CDCl_3): 23.03 (CH_3CO), 43.51 (CH_2), 55.84 (CH_3O), 78.94 (CH), 127.62 (C_4), 127.70 (2C_2 or 2C_3), 128.70 (2C_2 or 2C_3), 137.45 (C_1), 166.91 (COCH_3), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050, 935, 890, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1), 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61 (100).

Elemental analysis

Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$: 61.00% C; 6.83% H; 11.86% N.
60.91% C; 6.85% H; 11.66% N.

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EXAMPLE 20

Preparation of (D,L)- α -Acetamido-N-benzyl-2-(5-methylfuran)acetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8.0 mmol) was suspended in
5 anhydrous ethyl ether, and then boron trifluoride etherate (1.82 g, 12.8 mmol) was
rapidly added, and the resulting solution was stirred for 15 min. The
2-methylfuran (2.63 g, 32.0 mmol) was then added and the reaction was stirred at
10 room temperature (3 d). The reaction mixture was poured into an aqueous
saturated NaHCO₃ solution and extracted with ethyl acetate (3 x). The ethyl
acetate extracts were combined, dried (Na₂SO₄) and evaporated in vacuo to give a
beige solid, which was purified by flash chromatography (98:2
15 chloroform/methanol) to give the desired product as a white crystalline solid.
Yield: 1.40 g (61%)

R_f 0.25 (98:2 chloroform/methanol).

mp 148-150 °C.

20 ¹H NMR (DMSO-d₆) δ 1.88 (s, CII₃CO), 2.23 (s, CII₃), 4.24-4.36 (m, CH₂), 5.49 (d, J
= 8.0 Hz, CII), 6.01 (br s, C₃II), 6.14 (d, J = 2.4 Hz, C₄II), 7.20-7.31 (m, Ph), 8.52 (d,
J = 8.0 Hz, NII), 8.69 (t, J = 5.6 Hz, NII).

25 ¹³C NMR (DMSO-d₆) 13.44 (CH₃), 22.35 (CH₃CO), 44.11 (CH₂), 53.23 (CH), 107.51
(C₃' or C₄'), 110.40 (C₃' or C₄'), 128.13 (C₄''), 128.18 (2C₂'' or 2C₃''), 129.43 (2C₂''
or 2C₃''), 139.69 (C₁''), 149.18 (C₂' or C₅'), 153.81 (C₂' or C₅'), 170.78 (CH₃CO),
173.03 (CONII) ppm.

30 IR (KBr) 3270, 1620 (br), 1520 (br), 1440, 1360, 1210, 1010 cm⁻¹.

Mass spectrum, m/e (relative intensity) 286 (3), 179(8), 153 (57), 152 (57), 111 (23),
110 (100), 97 (23), 91 (31).

Elemental Analysis

35 Calculated: 67.12% C; 6.34% H; 9.78% N.

Found: 66.92% C; 6.52% H; 9.52% N.

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EXAMPLE 24

Preparation of (D,L)- α -Acetamido-N-benzyl-2-benzofuranacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (30 mL) and then boron trifluoride etherate (0.91 g, 6.3 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzofuran (1.89 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The reaction mixture was poured into an ice-cold saturated aqueous solution of NaHCO₃, and then the mixture was maintained at this temperature for an additional 15 min. The mixture was extracted with ethyl acetate (2 x), and the organic layers were combined, dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash chromatography (100% chloroform, then 99:1 chloroform/methanol) to yield the desired product.

Yield: 0.43 g (33%).

R_f 0.30 (98:2 chloroform/methanol).

mp 195-196 °C;

¹H NMR (DMSO-d₆) δ 1.94 (s, CH₃CO), 4.34 (d, J = 5.7 Hz, CH₂), 5.77 (d, J = 8.1 Hz, CH), 7.24-7.32 (m, C₃·II, C₅·II, C₆·II, Ph), 7.54 (d, J = 7.0 Hz, C₄·II or C₇·II), 7.62 (d, J = 7.0 Hz, C₁·II or C₇·II), 8.74 (d, J = 8.1 Hz, NII), 8.86 (t, J = 5.7 Hz, NII).

¹³C NMR (DMSO-d₆) 22.27 (CH₃CO), 42.30 (CH₂), 51.22 (CH), 104.34 (C_{3'}), 110.90 (C_{7'}), 121.05 (C_{4'}), 122.90 (C_{5'}), 124.28 (C_{6'}), 126.73 (C_{3'a}), 127.01 (2C_{2''} or 2C_{3''}), 127.69 (2C_{2''} or 2C_{3''}), 128.14 (C_{4''}), 138.87 (C_{1''}), 154.10 (C_{7'a}), 154.30 (C_{2'}), 167.40 (CH₃CO), 169.26 (CONH) ppm.

IR (KBr) 3230, 1625 (br), 1520 (br), 1440, 1090, 1085, 890, 735, 690 cm⁻¹;

Mass spectrum, m/e (relative intensity) 322 (5), 279 (1), 264 (1), 234 (1), 215 (5), 189 (45), 146 (100), 130 (11), 118 (7), 91 (87), 65 (16).

High resolution mass spectrum,

Calcd for C₁₉H₁₈N₂O₃ 322.1317.

Found 322.1318.

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EXAMPLE 22

Preparation of (D,L)- α -Acetamido-N-benzyl-2-benzos[b]thiophenacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (15 mL) and then boron trifluoride etherate (0.91 g, 6.3 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzo[b]thiophene (2.14 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The solution was poured into an ice-cold saturated aqueous solution of NaHCO₃, and then stirred for 15 min at 0 °C. The mixture was extracted with ethyl acetate (2 x), and the organic layers were combined, dried (Na₂SO₄) and evaporated in vacuo to give an orange oil. The oil was triturated with ethyl ether to yield a crystalline product which was filtered and further purified by flash chromatography (99:1 chloroform/methanol) to give the desired product.

Yield: 0.06 g (4%).

20 R_f 0.32 (99:1 chloroform/methanol).

mp 226-227 °C.

¹H NMR (DMSO-d₆) δ 1.94 (s, CH₃CO), 4.34 (d, J = 5.7 Hz, CH₂), 5.86 (d, J = 8.1 Hz, CII), 7.20-7.38 (m, C₃·II, C₆·II, C₇·II, PB), 7.77-7.80 (m, C₄·II or C₅·II), 25 7.89-7.93 (m, C₄·II or C₅·II), 8.76 (d, J = 8.1 Hz, NII), 8.97 (t, J = 5.7 Hz, NII).

¹³C NMR (DMSO-d₆) 22.34 (CH₃CO), 42.38 (CH₂), 52.70 (CH), 122.15 (C_{4'} or C_{7'}), 122.32 (C_{4'} or C_{7'}), 123.45 (C_{3'}), 124.37 (C_{5'} or C_{6'}), 124.41 (C_{5'} or C_{6'}), 126.89 (C_{4''}), 127.27 (2C_{2''} or 2C_{3''}), 128.27 (2C_{2''} or 2 C_{3''}), 138.84 (C_{3'a} or C_{7'a}), 138.95 (C_{3'a} or C_{7'a}), 142.58 (C_{1'}), 168.65 (CH₃CO), 169.12 (CONII) ppm. [A distinct signal for the C_{2'} carbon was not detected and is presumed to coincide with the C_{1'} carbon at 142.58 ppm].

35 IR (KBr) 3240, 1610 (br), 1510 (br), 1420, 1360, 1215, 1085, 885, 730, 710, 685 cm⁻¹.

Mass spectrum, m/e (relative intensity) 338 (8), 295 (2), 205 (76), 162 (100), 135 (22), 108 (12), 91 (59).

Elemental Analysis:

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1 Calculated: 67.43% C; 5.36% H; 8.28% N.
Found: 67.21% C; 5.37 %H; 8.12% N.

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EXAMPLE 23

Preparation of (D,L)- α -Acetamido-N-benzyl-3-indoleacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (0.69 g, 2.75 mmol) was suspended in anhydrous ethyl ether (20 mL) and then boron trifluoride etherate (0.63 g, 4.40 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The indole (1.30 g, 11.00 mmol) was then added and the reaction was stirred at room temperature (22 h). Petroleum ether (35-60 °C) was added to the reaction, and the resulting semisolid material filtered, and washed with petroleum ether (35-60 °C). Purification of the reaction mixture was accomplished by flash chromatography (98:2 chloroform/methanol) to produce the title compound as a white solid.

Yield: 0.25 g (18%).

R_f 0.14 (95:5 chloroform/methanol)

mp 213-214 °C.

1^H NMR (DMSO-d₆) δ 1.90 (s, CII₃CO), 4.36 (d, J = 6.0 Hz, CH₂), 5.72 (d, J = 7.2 Hz, CII), 6.90-7.37 (m, Ph, C₂·II), 7.02 (dd, J = 7.5 Hz, J = 7.5 Hz, C₅·II or C₆·II), 7.12 (dd, J = 7.5 Hz, J = 7.5 Hz, C₅·II or C₆·II), 7.39 (d, J = 7.5 Hz, C₄·II or C₇·II), 7.65 (d, J = 7.5 Hz, C₄·II or C₇·II), 7.86 (d, J = 7.2 Hz, NHCH), 8.13 (t, J = 6.0 Hz, NHCH₂), 10.30-10.80 (br s, NII).

¹³C NMR (DMSO-d₆) 22.32 (CH₃CO), 42.23 (CH₂), 49.98 (CH), 111.51 (C_{7'}), 112.08 (C_{3'}), 118.76 (C_{4'} or C_{6'}), 119.24 (C_{4'} or C_{6'}), 121.37 (C_{5'}), 123.94 (C_{2'}), 126.58 (C_{3'a}), 126.71 (C_{4''}), 127.33 (2C_{2''} or 2C_{3''}), 128.18 (2C_{2''} or 2C_{3''}), 136.28 (C_{7'a}), 139.44 (C_{1''}), 169.13 (CH₃CO), 170.81 (CONH) ppm.

IR (KBr) 3260, 1610 (br), 1515 (br), 1450, 1420, 1370, 1350, 1235, 1095, 895, 735, 715, 695, 600 cm⁻¹.

Mass spectrum, m/e (relative intensity) 321 (5), 278 (1), 264 (1), 233 (1), 214 (6), 187 (85), 171 (3), 145 (100), 118 (18), 91 (39).

Elemental Analysis:

Calculated: 71.01% C; 5.96% H; 13.06% N.

1 Found: 70.87% C; 6.15% H; 12.78% N.

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EXAMPLE 24

Preparation of (D, L)- α -Acetamido-N-benzyl-2-(5-methylpyrrole)acetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8 mmol) was suspended in anhydrous ethyl ether (175 mL), and then boron trifluoride etherate (1.38 g, 9.7 mmol) was added and the resulting solution stirred (15 min). The 2-methylpyrrole (0.85 g, 10 mmol) was then added and the reaction mixture was stirred under N₂ (6 d), during which time the color of the reaction mixture turned reddish brown and a dark-brown deposit formed at the bottom of the flask. The clear solution was decanted and treated with an aqueous saturated NaHCO₃ solution containing ice (100 mL) for 30 min. The aqueous reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried (Na₂SO₄) and the solvent removed in vacuo. The brown oily residue was purified by flash column chromatography using 98:2 chloroform/methanol as the eluent to yield the desired compound. The product was recrystallized from ethyl acetate/hexane to give a light yellow amorphous solid.

Yield 0.20 g (94%)

R_f 0.44 (95:5, chloroform/methanol).

mp 167-168 °C.

¹H NMR (DMSO-d₆) δ 1.87 (s, CII₃), 2.13 (s, COCII₃), 4.27 (br s, CII₂), 5.33 (d, J = 7.4 Hz, CII), 5.60 (s, C₄II), 5.77 (s, C₃II), 7.19-7.30 (m, 5 PhII), 8.22 (d, J = 7.4 Hz, NII), 8.45 (t, J = 5.5 Hz, NII), 10.38 (s, NII).

¹³C NMR (DMSO-d₆) 12.74 (CH₃), 22.49 (COCH₃), 42.11 (CH₂), 51.21 (CH), 105.09 (C₄), 106.07 (C₃), 126.16 (C₅), 126.64 (C_{4'}), 126.85 (C₂), 127.09 (2C_{2'} or 2C_{3'}), 128.17 (2C_{2'} or 2C_{3'}), 139.33 (C_{1'}), 168.88 (COCII₃), 169.79 (CONH) ppm.

IR (KBr) 3250, 1630, 1520, 1420, 1360, 1300, 1260, 1230, 1160, 1110, 1020 cm⁻¹.

Mass spectrum, m/e (relative intensity) 285 (M⁺, 10), 178 (20), 152 (24), 151 (100), 110 (12), 109 (93), 108 (22), 107 (25), 94 (16), 91 (43).

Elemental Analysis:

Calculated: 67.35% C; 6.71% H; 14.73% N.

1 Found: 67.57% C; 6.90% H; 14.52% N.

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1 Synthesis of Unsubstituted and Substituted- α -Acetamido-N-benzyl-2-furanacetamides.

General Procedure. 4-Methylmorpholine (1 equiv) was added to a solution of α -acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at -10 to -15 °C under N₂. After stirring (2 min), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10mL/10 mmol) was added over 5 min at -10 to -15 °C. The reaction mixture was allowed to stir at room temperature for 5 min and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated in vacuo, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization, or flash chromatography of the combined solid material. Examples 25-32 were prepared according to this procedure.

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EXAMPLE 25

(D,L)- α -Acetamido-N-benzyl-2-furanacetamide.

5 Using benzyl amine (0.27 g, 2.56 mmol) and racemic
 α -acetamido-2-furanacetic acid (0.47 g, 2.56 mmol) gave the desired compound.
The product was recrystallized from ethyl acetate to give a white solid.
Yield: 0.46 g (65%)

10 R_f 0.30 (98:2 chloroform/methanol).

mp 177-178 °C.

15 1H NMR (DMSO-d₆) δ 1.90 (s, CH₃), 4.31 (d, J = 6.0 Hz, CH₂), 5.58 (d, J = 8.1 Hz,
CH), 6.27 - 6.33 (m, C₃H), 6.40 - 6.44 (m, C₄H), 7.20 - 7.36 (m, 5 PhH), 7.60 - 7.64 (m,
C₅H), 8.57 (d, J = 8.1 Hz, NII), 8.73 (t, J = 6.0 Hz, NII).

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EXAMPLE 26

(D,L-)- α -Acetamido-N-(2-fluorobenzyl)-2-furanacetamide.

Using 2-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic
5 α -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.
Yield: 1.20 g (50%).

R_f 0.36 (96:4 chloroform/methanol).

mp 193-195 °C (recrystallized from EtOAc).

10 ¹H NMR (DMSO-d₆) δ 1.89 (s, COCH₃), 4.33 (d, J = 5.5 Hz, CH₂), 5.58 (d, J = 8.0 Hz,
CH), 6.28 (s, C₄H), 6.29 (s, C₃H), 7.62 (s, C₅H), 7.13-7.35 (m, 4 ArH), 8.61 (d, J = 8.0
Hz, NII), 8.76 (t, J = 5.5 Hz, NII).

15 ¹³C NMR (DMSO-d₆) 22.35 (COCH₃), 36.12 (d, J_{CF} = 6.6 Hz, CH₂), 50.88 (CHI),
107.64 (C₄), 110.43 (C₃), 115.04 (d, J_{CF} = 21.4 Hz, C_{3'}), 124.29 (d, J_{CF} = 4.2 Hz, C_{5'}),
125.64 (d, J_{CF} = 15.0 Hz, C_{1'}), 128.94 (d, J_{CF} = 9.0 Hz, C_{4'} or C_{6'}), 129.27 (d, J_{CF} =
5.5 Hz, C_{4'} or C_{5'}), 142.66 (C₅), 151.07 (C₂), 159.99 (d, J_{CF} = 244.4 Hz, C_{2'}), 168.17
20 (COCH₃), 169.24 (CONH) ppm.

IR (KBr) 3270, 1630, 1520, 1440, 1360, 1220, 1180, 1140, 1100, 1000, 740 cm⁻¹.

Mass spectrum, m/e (relative intensity) 291 (M⁺+1, 3), 274 (2), 247(3), 165 (4), 145
(10), 139 (98), 138 (46), 126 (7), 110 (10), 109 (65), 97 (93), 96 (100).

25 Elemental Analysis:

Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 62.20% C; 5.19% H; 9.69% N.

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EXAMPLE 27

(D,L)- α -Acetamido-N-(3-fluorobenzyl)-2-furanacetamide.

5 Making use of 3-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic α -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product. Yield 1.90 g (80%).

R_f 0.30 (96:4 chloroform/methanol).

10 mp 163-165 °C (recrystallized from ethyl acetate).

¹H NMR (DMSO-d₆) δ 1.89 (s, COCH₃), 4.31 (d, J = 5.5 Hz, C_{II}H), 5.55 (d, J = 7.8 Hz, CH), 6.31 (s, C₄H), 6.42 (s, C₃H), 6.98-7.37 (m, 4 ArH), 7.62 (s, C₅H), 8.61 (d, J = 7.8 Hz, NII), 8.70 (t, J = 5.5 Hz, NII).

15 ¹³C NMR (DMSO-d₆) 22.35 (COCH₃), 41.71 (CH₂), 51.01 (CH), 107.73 (C₄), 110.59 (C₃), 113.50 (d, J_{CF} = 21.6 Hz, C_{2'} or C_{4'}), 113.60 (d, J_{CF} = 22.3 Hz, C_{2'} or C_{4'}), 122.95 (br, C_{6'}), 130.18 (d, J_{CF} = 8.6 Hz, C_{5'}), 142.21 (d, J_{CF} = 7.5 Hz, C_{1'}), 142.66 (C₅), 151.03 (C₂), 162.28 (d, J_{CF} = 243.3 Hz, C_{3'}), 168.23 (COCH₃), 169.31 (CONH) ppm.

IR (KBr) 3230, 1630, 1540, 1440, 1360, 1220, 1140, 1000, 730 cm⁻¹.

Mass spectrum, m/e (relative intensity) 290 (M⁺, 71), 231 (7), 165 (18), 140 (23), 139 (100), 126 (16), 109 (6), 97 (118), 96 (100), 96 (30).

Elemental Analysis:

Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 61.97% C; 5.35% H; 9.53% N.

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EXAMPLE 28

(D,L)- α -Acetamido-N-(4-fluorobenzyl)-2-furanacetamide.

5 Using racemic α -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) and 4-fluorobenzylamine (1.13 g, 9.0 mmol) gave the desired product. Yield 2.10 g (88%).

R_f 0.30 (96:4 chloroform/methanol).

10 mp 188-190 °C (recrystallized from ethyl acetate).

¹H NMR (DMSO-d₆) δ 1.88 (s, COCH₃), 4.27 (d, J = 5.5 Hz, CH₂), 5.55 (d, J = 8.0 Hz, CH), 6.27 (s, 1H), 6.41 (s, 1H), 7.09-7.15 (m, 2ArH), 7.12-7.27 (m, 2 ArH), 7.61 (s, 1H), 8.58 (d, J = 8.0 Hz, NH), 8.75 (t, J = 5.5 Hz, NH).

15 ¹³C NMR (DMSO-d₆) 22.28 (COCH₃), 41.51 (CH₂), 50.87 (CH), 107.52 (C₄), 110.46 (C₃), 114.90 (d, J_{CF} = 21.1 Hz, C_{3'}), 129.48 (d, J_{CF} = 8.3 Hz, C_{2'}), 135.23 (d, J_{CF} = 3.2 Hz, C_{1'}), 142.53 (C₅), 151.08 (C₂), 161.12 (d, J_{CF} = 242.2 Hz, C_{4'}), 167.95 (COCH₃), 169.13 (CONH) ppm.

20 IR (KBr) 3230, 1620, 1500, 1360, 1320, 1260, 1210, 1140, 1000, 820, 780, 730 cm⁻¹.

Mass spectrum, m/e (relative intensity) 291 (M⁺+1, 4), 165 (4), 140 (9), 139 (92), 138 (52), 124 (6), 109 (71), 97 (60), 96 (100).

Elemental Analysis:

25 Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 61.76% C; 5.41% H; 9.43% N.

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EXAMPLE 29

(D, L)- α -Acetamido-N-(2,5-difluorobenzyl)-2-furanacetamide.

Using 2,5-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic α -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product. Yield 1.60 g (64%).

R_f 0.38 (96:4 chloroform/methanol).

mp 177-178 °C (recrystallized from ethyl acetate).

¹H NMR (DMSO-d₆) δ 1.89 (s, COCH₃), 4.31 (d, J = 5.5 Hz, CH₂), 5.55 (d, J = 7.7 Hz, CH), 6.32 (s, C₄H), 6.43 (s, C₃H), 7.22-7.25 (m, 3 ArH), 7.62 (s, C₅H), 8.62 (d, J = 7.7 Hz, NII), 8.78 (t, J = 5.5 Hz, NII).

¹³C NMR (DMSO-d₆) 22.30 (COCH₃), 35.98 (d, J_{CF} = 5.8 Hz, CH₂), 51.02 (CH), 107.81 (C₄), 110.58 (C₃), 115.06 (dd, J_{CF} = 19.5, 25.6 Hz, C_{3'} or C_{6'}), 115.16 (dd, J_{CF} = 15.6, 24.7 Hz, C_{3'} or C_{6'}), 116.52 (dd, J_{CF} = 10.1, 23.9 Hz, C_{4'}), 127.98 (dd, J_{CF} = 9.2, 17.7 Hz, C_{1'}), 142.69 (C₅), 150.78 (C₂), 155.89 (d, J_{CF} = 239.0 Hz, C_{2'} or C_{5'}), 158.18 (d, J_{CF} = 238.8 Hz, C_{2'} or C_{5'}), 168.38 (COCH₃), 169.35 (CONH) ppm.
IR (KBr) 3230, 1620, 1520, 1480, 1360, 1260, 1230, 1180, 1140, 1000, 860, 810, 730, 710 cm⁻¹.

Mass spectrum, m/e (relative intensity) 309 (M⁺+1, 1), 266 (1), 222(1), 165 (5), 140 (5), 139 (61), 138 (36), 127 (37), 97 (44), 96 (100).

Elemental Analysis:

Calculated: 58.44% C; 4.58% H; 9.09% N.

Found: 58.68% C; 4.69% H; 8.87% N.

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EXAMPLE 30

1. (D,L)- α -Acetamido-N-(2,6-difluorobenzyl)-2-furanacetamide.

Making use of 2,6-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic

α -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) the desired product was formed

5 Yield 1.90 g (73%).

mp 237-239 °C (recrystallized from ethanol).

^1H NMR (DMSO- d_6) δ 1.86 (COCH₃), 4.33 (d, J = 4.5 Hz, CH₂), 5.53 (d, J = 8.3 Hz,

10 CH), 6.17 (s, C₄H), 6.38 (s, C₃H), 7.05-7.10 (m, 2 ArH), 7.36-7.41 (m, 1 ArH), 7.60 (s, C₅H), 8.52 (d, J = 8.3 Hz, NII), 8.66 (t, J = 4.5 Hz, NII).

^{13}C NMR (DMSO- d_6) δ 22.33 (COCH₃), 30.74 (t, J_{CF} = 4.4 Hz, CH₂), 50.48 (CH), 107.24 (C₄), 110.40 (C₃), 111.61 (dd, J_{CF} = 8.0, 25.1 Hz, C_{3'}, C_{5'}), 113.67 (t, J_{CF} = 19.5 Hz, C_{1'}), 129.98 (t, J_{CF} = 10.5 Hz, C_{4'}), 142.50 (C₅), 151.23 (C₂), 160.93 (d, J_{CF} = 248.1, C_{2'} or C_{6'}), 161.10 (d, J_{CF} = 248.1 Hz, C_{2'} or C_{6'}), 167.59 (COCH₃), 169.00 (CONH) ppm.

IR (KBr) 3230, 1620, 1530, 1460, 1360, 1320, 1260, 1220, 1160, 1140, 1030, 1000, 820,
20 780, 750, 740, 710 cm⁻¹.

Mass spectrum, m/e (relative intensity) 309 (M⁺⁺¹, 4), 265 (2), 165 (4), 147 (7), 140 (8), 139 (87), 138 (36), 127 (54), 97 (58), 96 (100).

Elemental Analysis:

25 Calculated: 58.44% C; 4.58% H; 9.09% N.

Found: 58.62% C; 4.74% H; 8.99% N.

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EXAMPLE 31

(D)-(-)- α -Acetamido-N-benzyl-2-furanacetamide.

5 Starting with D- α -acetamido-2-furanacetic acid (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), the desired product was obtained.

Yield: 2.54 g (70%) The product was further recrystallized from ethyl acetate to give the title compound.

10 Yield: 2.30 g

mp 196-197 °C.

[α]²⁶D [c = 1, MeOH] = -78.3°. Addition of R(-)-mandelic acid to a CDCl₃ solution of the product gave only one signal for the acetamide methyl protons.

15 Mass spectrum, m/e (relative intensity) 272 (M⁺, 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63).

Elemental Analysis:

Calculated: 66.16% C; 5.92% H; 10.29% N.

20 Found: 66.09% C; 6.01% H; 10.38% N.

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EXAMPLE 32

(L)-(+)- α -Acetamido-N-benzyl-2-furanacetamide.

Using L- α -acetamido-2-furanacetic acid (2.83 g, 15.46 mmol) and benzylamine (1.65 g, 15.46 mmol) gave 3.80 g of the enriched desired product. ¹H NMR analysis with R(-)-mandelic acid showed that it was greater than 80% enriched in the title compound. The pure L-enantiomer was obtained by recrystallization from absolute ethanol.

10 Yield: 1.60 g.

mp 196-197 °C.

$[\alpha]^{26}_D [c = 1, \text{MeOH}] = +79.0^\circ$.

15 Mass spectrum, m/e (relative intensity) 273 ($M^+ + 1$, 3), 229 (2), 214 (2), 184 (1), 165 (7), 157 (4), 140 (33), 139 (100), 138 (95), 97(98), 96 (100), 91 (98).

Elemental Analysis:

Calculated: 66.16% C; 5.92% H; 10.29% N.

20 Found: 65.89% C; 5.86% H; 10.42% N.

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EXAMPLE 33

Resolution of (D, L)- α -Acetamido-2-furanacetic acid Using

(R)-(+) α -Methylbenzylamine and (S)-(-) α -Methylbenzylamine.

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(R)-(+) α -Methylbenzylamine (13.22 g, 0.11 mol) was added to an absolute ethanol solution (550 mL) of racemic α -acetamido-2-furanacetic acid (20.00 g, 0.11 mol). The resulting solution was cooled in the freezer overnight. The white precipitate (12.00 g) which separated upon cooling was filtered, and the mother liquid evaporated to give a salt which was later used for obtaining L- α -acetamido-2-furanacetic acid. The initial salt was recrystallized (3 x) from absolute ethanol to yield 4.00 g of the pure diasteromeric salt.
mp 173-175°C.

$[\alpha]^{26}_D [c=1, \text{MeOH}] = -108^\circ$

20 Elemental Analysis

Calculated: 63.14% C; 6.62% H; 9.21% N.

Found: 63.19% C; 6.62% H; 9.12% N.

The purified salt was treated with 5% aqueous NH_4OH solution,

25 extracted with ethyl ether (3 x 50 mL), and then acidified with a 8.5% aqueous solution of H_3PO_4 and then extracted with ethyl acetate (3 x 100 mL) to yield 2.45 g (25%) of D- α -acetamido-2-furanacetic acid.

30 mp 169-171°C.

$[\alpha]^{26}_D [c=1, \text{MeOH}] = -184.2^\circ$

Elemental Analysis:

Calculated: 52.46% C; 4.95% H; 7.65% N.

35 Found: 52.17% C; 4.89% H; 7.56% N.

The salt obtained after evaporation of the main mother

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1 liquor was hydrolysed with 5% aqueous NH_4OH solution to give
10.10 g of the enriched L- α -acetamido-2-furanacetic acid
 $[\alpha]^{26}\text{D}[\text{c}=1, \text{MeOH}] = +47.7^\circ$. (S)-(-) -methylbenzylamine (6.70
5 g, 0.055 mol) was added to a solution of enriched L- α -acetamido-
2-furanacetic acid (10.10 g, 0.055 mol) in absolute ethanol
(275 mL). The white precipitate of the diastereomeric salt
10 (8.10 g) that separated upon cooling the solution in the
freezer (1 h) was filtered. The salt was recrystallized
from absolute ethanol (3 x) to yield 3.00g of the salt,
mp 172-174 °C.

15 $[\alpha]^{26}\text{D}[\text{c}=1, \text{MeOH}] = +106^\circ$.

Elemental Analysis:

Calculated: 63.14% C; 6.62% H; 9.21% N.

Found: 63.18% C; 6.47% H; 9.00% N.

20 The salt from the third recrystallization was treated
with a 5% aqueous NH_4OH solution and extracted with ethyl ether
(3 x 50 mL), and then acidified with a 8.5% aqueous solution
of H_3PO_4 , and then extracted with ethyl acetate (3
25 x 100 mL) to give 1.63g (32%) of L- α -acetamido-2-furanacetic
acid.

mp 169-171 °C.

$[\alpha]^{26}\text{D}[\text{c}=1, \text{MeOH}] = +182^\circ$.

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EXAMPLE 34

Enzymatic Separation of D(-)- α -acetamido-2-furanacetic acid (R-19) from DL (\pm)- α -acetamido-2-furanacetic acid.

DL (\pm)- α -acetamido-2-furanacetic acid (2.00 g, 10.9 mmol) was suspended in deionized H₂O (600mL). An aqueous solution of LiOH (1N) was added to this suspension dropwise until all of the acid had dissolved and the pH was 7.2. Acylase I, Grade II (20 mg, activity = 900 units/mg, Sigma Chemical Company, Cat. No. A 8376) was then added to the above solution and the mixture stirred at 34-37°C (41h). The suspension was then cooled to room temperature and acidified to pH 1.5 with aqueous 1N HCl. The suspended material was filtered, and the filtrate was saturated with solid NaCl, and then extracted with ethyl acetate (3x250 mL). The combined ethyl acetate extracts was dried (Na₂SO₄). The solvent was removed in vacuo and the residue was triturated with ethyl acetate (10mL). The white solid (0.75 g) that remained was filtered and was pure D(-)- α -acetamido-2-furanacetic acid; mp 168-169°C, mixed mp with an authentic sample 168-169°C; [d]_D²⁶ [c=1, MeOH] = -184.3°.

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EXAMPLE 35

Preparation of D,L- α -Acetamido-2-furanacetic Acid.

An ethereal solution of $ZnCl_2$ (1 N, 28 mL, 0.028 mol) was added to a stirred
5 solution of ethyl acetamido-2-bromoacetate (4.40 g, 0.019 mol) and furan (11.23 g,
0.165 mol) in dry tetrahydrofuran (100 mL), and allowed to stir at room
temperature (5 h). The mixture was then treated with H_2O (50mL), the organic
10 phase separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The
organic layers were combined, dried (Na_2SO_4) and the volatile materials were
removed by distillation in vacuo to give approximately 4.00 g (97%) of light-brown
15 semi-solid material. TLC analysis showed a major spot at R_f 0.30 (99:1
chloroform/methanol). The desired compound, D,L-ethyl
silica gel using 99:1 chloroform/methanol as the eluent to give 3.60 g (87%) of a
beige solid.

mp 68-70 °C.

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D, L-Ethyl α -acetamido-2-furanacetate (4.00 g, 19 mmol) was dissolved in
90:10 ethanol/water (150 mL) and then KOH (2.00 g, 35 mmol) was added and the
resulting solution stirred at room temperature (48 h). The reaction was
25 concentrated in vacuo and the residue diluted with H_2O and then washed with
ethyl ether (3 x 50 mL). The aqueous layer was then made acidic with a 8.5%
aqueous solution of H_3PO_4 and extracted with ethyl acetate (3 x 150 mL). The
30 organic layers were combined, dried (Na_2SO_4), evaporated to dryness in vacuo to
give the desired compound.

Yield: 2.65 g (76%).

R_f 0.37 (8:1:1 isopropanol/ NH_4OH / H_2O).

35 mp 172-174 °C.

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EXAMPLE 36

Synthesis of (D,L)-2-Acetamido-4-pentenoic Acid-N-benzylamide.

4-Methylmorpholine (0.55 g, 5.40 mmol) was added to a stirred solution of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol) in dry tetrahydrofuran (60 mL) at -10 to -15 °C under N₂. After stirring (2 min), isobutyl chloroformate (0.75 g, 5.70 mmol) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of benzylamine (0.61 g, 5.70 mmol) in tetrahydrofuran (10 mL) was added slowly at -10 to -15 °C. After stirring (5 min) at room temperature, the insoluble salt was removed by filtration. The filtrate was evaporated to dryness and the residue was triturated with ethyl acetate, and the remaining white solid was filtered to yield the desired product.

Yield 0.81 g (64%).

R_f 0.36 (4% methanol/chloroform).

mp 118-120 °C (recrystallized from ethyl acetate/cyclohexane).

¹H NMR (DMSO-d₆) δ 1.83 (s, COCH₃), 2.22-2.49 (m, CH₂CH=CH₂), 4.26 (d, J = 5.3 Hz, CH₂ Ph), 4.25-4.33 (m, CII), 4.99-5.09 (m, CH₂CH=CH₂), 7.21-7.29 (m, 5 PhII), 8.05 (d, J = 7.6 Hz, NII), 8.46 (br s, NII).

¹³C NMR (DMSO-d₆) 22.41 (COCH₃), 36.24 (CH₂CH=CH₂), 41.91 (CH₂Ph), 52.20 (CH), 117.15 (CH₂CH=CH₂), 126.54 (C_{4'}), 126.99 (2C_{2'} or 2C_{3'}), 128.04 (2C_{2'} or 2C_{3'}), 134.25 (CH₂CH=CH₂), 139.22 (C_{1'}), 169.02 (COCH₃), 170.96 (CONH) ppm.

Mass spectrum, m/e (relative intensity) 246 (M⁺, 4), 205 (4), 163 (15), 140 (8), 106 (33), 91 (77), 70 (100).

Elemental Analysis:

Calculated:

68.27% C; 7.37% H; 11.37% N.

Found:

68.55% C; 7.31% H; 11.48% N.

1 Mass spectrum m/e (relative intensity) 292 ($M^{++}1$, 1), 233 (8), 158 (19), 157 (100),
116 (26), 115 (100), 106 (29), 91 (72).

Elemental Analysis:

5 Calculated: 61.84% C; 7.26% H; 14.42% N.
 Found: 61.67 % C; 7.10% H; 14.14% N.

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EXAMPLE 37

Synthesis of (D,L)-2-Acetamido-N-benzyl-2-(1-morpholine)acetamide.

A mixture of ethyl 2-acetamido-2-(1-morpholine)acetate (0.59 g, 2.56 mmol), benzylamine (0.28 g, 2.82 mmol) and sodium cyanide (0.01 g, 0.26 mmol) in methanol (5 mL) was stirred at 50-55 °C for 18 hr. The solvent was removed in vacuo and the residue triturated with ethyl acetate (5 mL). The white solid (0.35 g) that remained was collected by filtration and identified as the desired compound.

10 The filtrate was concentrated and the residue purified by flash column chromatography (2% methanol/chloroform) on SiO₂. The initial fractions gave a trace amount (0.09 g) of (D,L)-2-acetamido-N-benzyl-2-(N-benzylamine)acetamide. Continued elution gave additional amounts (0.20 g) of the title compound.

15 (D,L)-2-Acetamido-N-benzyl-2-(N-benzylamine)acetamide:

Yield: 0.09 g (11%).

mp 135-138 °C.

20 ¹H NMR (DMSO-d₆) δ 1.83 (s, COCH₃), 3.56 (d, J = 13.6 Hz, NHClI), 3.66 (d, J = 13.6 Hz, NHClI), 4.23 (d, J = 5.4 Hz, CH₂), 4.89 (d, J = 8.0 Hz, ClI), 7.05-7.38 (m, 10 PhII), 8.20 (d, J = 8.0 Hz, NH), 8.51 (t, J = 5.4 Hz, NH).

25 ¹³C NMR (DMSO-d₆) 22.63 (COCH₃), 42.11 (CH₂), 48.57 (NHCH₂), 64.41 (CH), 126.65 (C₄), 126.70 (C_{4'}), 127.13, 128.00, 128.13, 128.22, 139.24 (C₁ or C_{1'}), 140.12 (C₁ or C_{1'}), 169.61 (COCH₃), 169.90 (CONH) ppm.

(D,L)-2-Acetamido-N-benzyl-2-(1-morpholine)acetamide.

Yield: 0.48 g (64%).

30 R_f 0.35 (4% methanol/chloroform).

mp 171-172 ° (recrystallized from ethyl acetate).

35 ¹H NMR (DMSO-d₆) δ 1.86 (s, COCH₃), 2.30-2.40 (m, CH₂NCH₂), 3.51 (br s, CH₂OCH₂), 4.18-4.33 (m, CH₂), 5.07 (d, J = 8.9 Hz, CH), 7.18-7.25 (m, 5 PhII), 8.23 (d, J = 8.9 Hz, NII), 8.58 (br s, NII).

¹³C (DMSO-d₆) 22.39 (COCH₃), 42.20 (CH₂), 48.43 (CH₂NCH₂), 66.03 (CH), 69.24 (CH₂OCH₂), 126.76 (C_{4'}), 127.13 (2C_{2'} or 2C_{3'}), 128.23 (2C_{2'} or 2C_{3'}), 139.42 (C_{1'}),

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EXAMPLE 38

Synthesis of (D,L)-Ethyl 2-acetamido-2-(ethylamino)acetate.

A cold (-78 °C) solution of ethyl 2-acetamido-2-bromoacetate (2.10 g, 9.38 mmol) in dry tetrahydrofuran (80 mL) was added slowly into a cooled (-78 °C) tetrahydrofuran (20 mL) solution of methylamine (1.40 g, 31.04 mmol) over a period of 20 min. The reaction was stirred at -78 °C (1 h), and then at room temperature (1 h). The precipitated salt was filtered and the filtrate concentrated.

The residue was purified by flash column chromatography on SiO₂ using 3% methanol/chloroform as the eluent to yield the desired compound as a light yellow oil.

Yield: 0.90 (51%).

R_f 0.36 (4% methanol/chloroform).

¹H NMR (CDCl₃) 0.93 (t, J = 6.7 Hz, NHCH₂CH₃), 1.12 (t, J = 6.8 Hz, OCH₂CH₃), 1.87 (s, COClH₃), 2.48 (q, J = 6.7 Hz, NHCH₂CH₃), 4.05 (q, J = 6.8 Hz, OCH₂CH₃), 5.05 (d, J = 7.1 Hz, CII), 7.09 (d, J = 7.1 Hz, NII).

¹³C NMR (CDCl₃) 13.64 (NHCH₂CH₃), 14.55 (OCH₂CH₃), 22.53 (COCH₃), 39.06 (NHCH₂CH₃), 61.38 (CH), 64.14 (OCH₂CH₃), 170.09 (COCH₃), 170.20 (COOCH₂CH₃) ppm.

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EXAMPLE 39

Using the procedures described herein, the following examples are also prepared:

(D,L)-Acetamido-N-benzyl-3-furanacetamide

5 (D,L)-Acetamido-N-(2-fluorobenzyl)-3-furanacetamide

(D,L)-Acetamido-N-(3-fluorobenzyl)-3-furanacetamide

(D,L)-Acetamide-N-(4-fluorobenzyl)-3-furanacetamide

-Acetamide-N-benzyl-2-aminoacetamide

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1 Preparation of α -Heteroatom Substituted Amino Acids. Synthesis of Ethyl 2-Acetamido-2-substituted Acetates. General Procedure.

5 A cooled (-78 °C) solution of ethyl 2-bromo-2-acetamidoacetate (1 equiv) in THF (1 mmol/10 mL) was added slowly to a THF (1 mmol/4 mL) solution of the nitrogen nucleophile (5-10 equiv) at -78 °C. The reaction was stirred at this temperature (0.5 h) and then at room temperature (1 h). The insoluble materials
10 were filtered and washed with THF. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on SiO₂ gel (using the indicated solvent as the eluent) to give the desired product.

15 Using this procedure the following examples were prepared.

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EXAMPLE 40

1 Synthesis of Ethyl 2-Acetamido-2-aminoacetate.

5 Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and liquid NH₃ (5-6 equiv) yielded a light brown residue, which on purification by flash column chromatography on SiO₂ gel (5% MeOH/CHCl₃) gave the desired product as a yellow oil.

10 Yield: 1.00 g (70%).

R_f 0.21 (5% MeOH/CHCl₃).

15 ¹H NMR (CDCl₃) δ 1.31 (t, J = 7.1 Hz, 3 H), 2.03 (s, 3 H), 2.61 (br s, 2 H), 4.24 (q, J = 7.1 Hz, 2 H), 5.21 (d, J = 7.1 Hz, 1 H), 7.50 (d, J = 7.1 Hz, 1 H).

20 ¹³C NMR (CDCl₃) 13.72, 22.68, 59.70, 61.73, 170.40, 170.68 ppm.

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EXAMPLE 41

1 Synthesis of Ethyl 2-Acetamido-2-(methylamino)acetate.

Use of ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and MeNH₂ (2.50 g, 80.6 mmol) gave an oily residue (1.50 g). The residue was purified by flash column chromatography on SiO₂ gel (3% MeOH/CHCl₃) to yield the desired product as an oil.

Yield: 1.00 g (65%).

10 ¹H NMR (CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3 H), 2.07 (s, 3 H), 2.36 (s, 3 H), 4.26 (q, J = 7.1 Hz, 2 H), 5.20 (d, J = 7.4 Hz, 1 H), 6.60 (br s, 1 H).

13C NMR (CDCl₃) 14.02, 23.06, 30.84, 62.04, 65.72, 170.09, 170.40 ppm.

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EXAMPLE 42

1 Synthesis of Ethyl 2-Acetamido-2-(N,N-dimethylamino)acetate.

Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and Me₂NH (5-6 equiv) gave the desired product as a yellow oil.

5 Yield: 1.50 g (89%).

¹H NMR (CDCl₃) δ 1.25 (t, J = 7.1 Hz, 3 H), 2.02 (s, 3 H), 2.23 (s, 6 H), 4.10-4.25 (m, 2 H), 5.24 (d, J = 8.3 Hz, 1 H), 6.59 (d, J = 8.3 Hz, 1 H).

¹³C NMR (CDCl₃) 14.05, 23.00, 40.28 (2 C), 61.84, 69.24, 169.38, 170.57 ppm.

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EXAMPLE 43

1 Synthesis of Ethyl 2-Acetamido-2-(4-morpholine)acetate.

Using morpholine (1.71 g, 19.64 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) gave an oily residue, which was purified by flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give the desired product as a thick oil.

5 Yield: 1.90 g (93%).

R_f 0.29 (3% MeOH/CHCl₃).

10 ¹H NMR (CDCl₃) δ 1.32 (t, J = 6.8 Hz, 3 H), 2.07 (s, 3 H), 2.43-2.72 (m, 4 H), 3.58-3.78 (m, 4 H), 4.26 (q, J = 6.8 Hz, 2 H), 5.27 (d, J = 7.9 Hz, 1 H), 6.39 (d, J = 7.9 Hz, 1 H).

15 ¹³C NMR (CDCl₃) 14.21, 23.25, 48.47 (2 C), 62.06, 66.71 (2 C), 69.22, 169.00, 170.46 ppm.

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EXAMPLE 44

1 Synthesis of Ethyl 2-Acetamido-2-(N-anilino)acetate.

5 Use of aniline (1.83 g, 19.6 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) provided a brown residue which was purified by flash column chromatography on SiO₂ gel (CHCl₃-2% MeOH/CHCl₃ gradient) to yield the desired product.

Yield: 1.80 g (85%).

R_f 0.52 (4% MeOH/CHCl₃).

10 mp 87-89 °C (recrystallized from ethyl acetate/petroleum ether).

15 ¹H NMR (CDCl₃) δ 1.29 (t, J = 7.1 Hz, 3 H), 1.84 (s, 3 H), 4.27 (q, J = 7.1 Hz, 2 H), 5.89 (d, J = 8.2 Hz, 1 H), 6.43 (d, J = 8.2 Hz, 1 H), 6.68-6.71 (m, 2 H), 6.80-6.83 (m, 1 H), 7.17-7.22 (m, 2 H). The remaining amino proton was not detected.

20 ¹³C NMR (CDCl₃) 13.96, 22.98, 60.19, 62.41, 113.87 (2 C), 119.29, 129.37 (2 C), 144.09, 169.77, 170.14 ppm.

IR (KBr) 3340, 1720, 1635, 1590, 1490, 730, 710 cm⁻¹.

25 Mass spectrum (FD) 237 (M⁺⁺¹).

Elemental analysis

Calculated for C₁₂H₁₆N₂O₃ 61.00% C; 6.83% H; 11.86% N.

Found 60.88% C; 6.56% H; 12.00% N.

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EXAMPLE 45

1 Synthesis of Ethyl 2-Acetamido-2-(N-(3-pyrazolylamino))acetate.

Using ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.92 mmol) and 3-aminopyrazole (1.85 g, 22.32 mmol) and purification of the reaction product by chromatography on SiO₂ gel (2% MeOH/CHCl₃) gave the desired product as a yellow oil.

Yield: 1.80 g (89%).

R_f 0.35 (8% MeOH/CHCl₃).

10 ¹H NMR (CDCl₃) δ 1.21 (t, J = 7.1 Hz, 3 H), 1.89 (s, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 1.8 Hz, 1 H), 5.71 (br s, 1 H), 5.73 (d, J = 7.1 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 1 H), 7.98 (d, J = 7.1 Hz, 1 H). The remaining amino proton was not detected.

15 ¹³C NMR (CDCl₃) 13.73, 22.49, 61.41, 62.02, 91.79, 130.53, 153.02, 169.96, 170.93 ppm.

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EXAMPLE 46

1 Synthesis of Ethyl 2-Acetamido-2-(N-hydroxyamino)acetate.

5 Using ethyl 2-bromo-2-acetamidoacetate (2.10 g, 9.37 mmol) and
anhydrous NH₂OH (0.93 g, 28.00 mmol) gave an oily residue. The residue was
purified by flash column chromatography on SiO₂ gel (5% MeOH/CHCl₃) to give
the desired product. The product was recrystallized from EtOH to give a white
flaky solid.

10 Yield: 1.00 g (61%).

15 R_f 0.24 (5% MeOH/CHCl₃).

mp 119-121 °C.

20 ¹H NMR (DMSO-d₆) δ 1.19 (t, J = 6.9 Hz, 3 H), 1.87 (s, 3 H), 4.10 (q, J = 6.9 Hz, 2 H),
5.09 (dd, J = 4.0, 8.0 Hz, 1 H), 6.06 (br s, 1 H), 7.63 (s, 1 H), 8.50 (d, J = 8.0 Hz,
1 H).

25 ¹³C NMR (DMSO-d₆) 14.05, 22.46, 60.82, 67.37, 169.19, 169.48 ppm.
IR (KBr) 3300, 1750, 1660, 1540, 1390, 610 cm⁻¹.

30 Mass spectrum (FD) 177 (M⁺⁺1).

35 Elemental analysis

Calculated for C₆H₁₂N₂O₄ 40.91% C; 6.87% H; 15.90% N.

Found 40.79% C; 6.87% H; 15.90% N.

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EXAMPLE 47

- 1 Synthesis of Ethyl 2-Acetamido-2-(N-(N-methylhydroxymethyl)amino)acetate.

5 MeNHOH (17.39 mmol) (prepared from MeNHOH-HCl (2.00 g, 23.95 mmol) and NaOMe (0.94 g, 17.39 mmol)), and ethyl 2-bromo-2-acetamidoacetate (1.00 g, 4.46 mmol) gave an oily residue. The residue was triturated with EtOAc (5 mL) and the solid that remained was filtered and recrystallized from EtOH to give the desired product as a white solid.

10 Yield: 0.70 g (82%).

15 R_f 0.34 (5% MeOH/CHCl₃).

20 mp 148-150 °C.

25 ¹H NMR (DMSO-d₆) δ 1.17 (t, J = 7.0 Hz, 3 H), 1.89 (s, 3 H), 2.37 (s, 3 H), 4.00-4.20 (m, 2 H), 5.04 (d, J = 9.2 Hz, 1 H), 8.17 (s, 1 H), 8.43 (d, J = 9.2 Hz, 1 H).

30 ¹³C NMR (DMSO-d₆) 14.04, 22.28, 43.78, 50.79, 71.46, 168.29, 170.23 ppm.

35 IR (KBr) 3320, 3200 (br), 1760, 1660, 1530, 1470, 720, 640 cm⁻¹.

40 Mass spectrum (FD) 192 (M⁺⁺1).

45 Elemental analysis

Calculated for C ₇ H ₁₄ N ₂ O ₄ ·0.25 H ₂ O	43.18% C; 7.51% H; 14.39% N.
Found	43.28% C; 7.25% H; 14.64% N.

EXAMPLE 48

1 Synthesis of Ethyl 2-Acetamido-2-(N-(N,O-dimethylhydroxyamino))acetate.

5 MeNHOMe (17.40 mmol) (prepared from MeNHOMe-HCl (2.18 g, 22.32 mmol) and NaOMe (0.94 g, 17.40 mmol)) and ethyl 2-bromo-2-acetamidoacetate (1.00 g, 4.46 mmol) gave a residue which was purified by flash column chromatography on SiO₂ gel (1% MeOH/CHCl₃) to give the desired product as an oil.

Yield: 0.60 g (66%).

10 R_f 0.53 (2% MeOH/CHCl₃).

15 ¹H NMR (CDCl₃) δ 1.35 (t, J = 7.0 Hz, 3 H), 2.12 (s, 3 H), 2.62 (s, 3 H), 3.46 (s, 3 H), 4.30 (q, J = 7.0 Hz, 2 H), 5.36 (d, J = 8.9 Hz, 1 H), 6.66 (d, J = 8.9 Hz, 1 H).

20 ¹³C NMR (CDCl₃) 14.06, 22.89, 40.30, 60.01, 61.89, 70.16, 168.14, 170.53 ppm.

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1 Synthesis of 2-Acetamido-N-benzyl-2-substituted Acetamides. General Procedure.

5 A mixture of the ethyl 2-substituted-2-acetamidoacetate (1 equiv), benzylamine (1.2 equiv), and NaCN (0.1 equiv) in MeOH (1 mmol/25 mL) was stirred at 45-50 °C (18 h). The solvent was removed in vacuo and the residue was purified using either trituration with EtOAc or flash column chromatography on SiO₂ gel with the indicated solvent as the eluent.

10 Using this procedure the following examples were prepared.

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EXAMPLE 49

1 Synthesis of 2-Acetamido-N-benzyl-2-aminoacetamide.

5 Ethyl 2-acetamido-2-aminoacetate (1.00 g, 6.25 mmol), benzylamine (0.80 g, 7.5 mmol) and NaCN (0.03 g, 0.61 mmol) gave a residue which solidified on standing (18 h). The reaction mixture was triturated with EtOAc (20 mL). The white solid which remained was filtered and then further purified by recrystallization from EtOAc.

Yield: 1.00 g (72%).

10 R_f 0.21 (5% MeOH/CHCl₃).

mp 131-133 °C (dec.).

15 ¹H NMR (DMSO-d₆) δ 1.83 (s, 3 H), 2.35 (br s, 2 H), 4.28 (d, $J = 4.4$ Hz, 2 H), 4.91 (d, $J = 7.0$ Hz, 1 H), 7.20-7.32 (m, 5 H), 8.31 (br s, 1 H), 8.51 (br s, 1 H).

13C NMR (DMSO-d₆) 22.66, 42.05, 60.29, 126.67, 127.10 (2 C), 128.18 (2 C), 139.23, 169.24, 170.67 ppm.

IR (KBr) 3300, 1650 (br), 1530 (br), 1450, 740 cm⁻¹.

20 Mass spectrum, m/e (relative intensity) 222 ($M^{+}+1$, 100), 221 (M^{+} , 29), 133 (8).
Elemental analysis

Calculated for C₁₁H₁₅N₃O₂ 59.71% C; 6.83% H; 18.99% N.

Found

59.86% C; 6.88% H; 18.72% N.

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EXAMPLE 50

Synthesis of 2-Acetamido-N-benzyl-2-(methylamino)acetamide

Ethyl 2-acetamido-2-(methylamino)acetate (1.50 g, 8.63 mmol), benzylamine (1.11 g, 10.35 mmol) and NaCN (0.04 g, 0.82 mmol) gave a brown residue which was purified by flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to yield the desired product.

Yield: 1.00 g (49%).

R_f 0.33 (3% MeOH/CHCl₃).

mp 115-117 °C (recrystallized from ethyl acetate/petroleum ether).

¹H NMR (DMSO-d₆) δ 1.87 (s, 3 H), 2.18 (s, 3 H), 4.20-4.29 (m, 2 H), 4.87 (d, J = 7.9 Hz, 1 H), 7.24-7.35 (m, 5 H), 8.14 (d, J = 7.9 Hz, 1 H), 8.55 (br s, 1 H). The remaining amino proton was not detected.

¹³C NMR (DMSO-d₆) 22.52, 31.37, 42.04, 65.99, 126.68, 127.12 (2 C), 128.18 (2 C), 139.28, 169.51, 169.83 ppm.

IR (KBr) 3240, 1610 (br), 1500 (br), 1430, 725, 670 cm^{-1} .

Elemental analysis

Calculated for C₁₂H₁₇N₃O₂: 61.26% C; 7.28% H; 17.88% N

Found 61.12% C; 7.01% H; 17.71% N

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EXAMPLE 51

- ## 1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylamino)acetamide.

Using ethyl 2-acetamido-2-(ethylamino)acetate (0.90 g, 4.79 mmol), benzylamine (0.62 g, 5.75 mmol), and NaCN (0.03 g, 0.51 mmol) gave an oily residue which was purified by flash column chromatography on SiO₂ gel (3% MeOH/CHCl₃) to give the desired product as a white solid.

Yield: 0.35 g (29%).

R_f 0.34 (4% MeOH/CHCl₃)

10 mp 123-125 °C (recrystallized from ethyl acetate/hexane).

¹H NMR (DMSO-d₆) δ 0.93 (t, J = 6.8 Hz, 3 H), 1.81 (s, 3 H), 2.08 (br s, 1 H), 2.40-2.48 (m, 2 H), 4.22 (d, J = 5.5 Hz, 2 H), 4.90 (d, J = 7.8 Hz, 1 H), 7.20-7.27 (m, 5 H), 8.08 (d, J = 7.8 Hz, 1 H), 8.48 (t, J = 5.5 Hz, 1 H).

¹³C NMR (CDCl₃) 15.14, 22.97, 37.65, 43.53, 65.68, 127.44 (2 C), 127.50, 128.64 (2 C), 137.73, 169.75, 171.20 ppm.

IR (KBr): 3250, 1620 (br), 1510 (br), 1450 (br), 740, 680 cm^{-1}

Elemental analysis

Calculated for C₁₂H₁₈N₂O₂: 62.62% C; 7.62% H.

Found 62.68% C; 7.40% H; 10.81% N.

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EXAMPLE 52

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-anilino)acetamide.

Employing ethyl 2-acetamido-2-(N-anilino)acetate (2.00 g, 8.47 mmol), benzylamine (1.09 g, 10.00 mmol), and NaCN (0.04 g, 0.84 mmol) gave a white 5 solid which separated during the course of the reaction. The precipitate was filtered and purified by recrystallization from absolute EtOH to give the desired product.

Yield: 1.10 g (44%).

10 mp 183-185 °C.

¹H NMR (DMSO-d₆) δ 1.84 (s, 3 H), 4.31 (d, J = 5.8 Hz, 2 H), 5.67 (t, J = 8.1 Hz, 1 H), 6.04 (d, J = 8.1 Hz, 1 H), 6.59-6.64 (m, 1 H), 6.70-6.72 (m, 2 H), 7.06-7.11 (m, 2 H), 7.20-7.33 (m, 5 H), 8.41 (d, J = 8.1 Hz, 1 H), 8.72 (t, J = 5.8 Hz, 1 H).

15 ¹³C NMR (DMSO-d₆) 22.46, 42.25, 60.42, 113.21 (2 C), 117.22, 126.72, 127.16 (2 C), 128.18 (2 C), 128.77 (2 C), 138.99, 145.88, 168.65, 169.70 ppm.

IR (KBr) 3270, 1630, 1520, 1490, 1430, 740, 690 cm⁻¹.

20 Mass spectrum, m/e (relative intensity) 297 (M⁺, 2), 239 (7), 164 (28), 163 (100), 122 (20), 121 (100), 106 (47), 104 (65), 93 (63), 91 (77).

Elemental analysis

Calculated for C₁₇H₁₉N₃O₂ 68.67% C; 6.44% H; 14.13% N.

25 Found 68.94% C; 6.42% H; 13.92% N.

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EXAMPLE 53

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-(3-pyrazolylamino))acetamide.

A solution of ethyl 2-acetamido-2-(N-(3-pyrazolylamino))acetate (1.60 g, 7.1 mmol) in MeOH (40 mL) containing benzylamine (0.83 g, 7.8 mmol) and 5 NaCN (50 mg, 1 mmol) was stirred at 45-55 °C (18 h). TLC analysis (8% MeOH/CHCl₃) of the reaction mixture indicated the presence of only a minor amount of product. A second lot of NaCN (50 mg, 1 mmol) was then added and the reaction was allowed to proceed at 45-55 °C (6 h) and then at room temperature 10 (48 h). The solvent was removed in vacuo and the residue was triturated with EtOAc (15 mL). The insoluble solid that remained was filtered and purified by flash column chromatography on SiO₂ gel (7% MeOH/CHCl₃) to give the desired product.

15 Yield: 0.90 g (44%).

R_f 0.35 (8% MeOH/CHCl₃).

mp 135-137 °C.

¹H NMR (DMSO-d₆) δ 1.82 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.51-5.55 (m, 3 H), 7.18-7.40 (m, 6 H), 8.36 (br s, 1 H), 8.53 (br s, 1 H), 11.66 (br s, 1 H).

¹³C NMR (DMSO-d₆) 22.59, 42.29, 61.79, 90.68, 126.67, 127.07 (2 C), 128.17 (2 C), 129.10, 139.41, 153.53, 169.19, 169.67 ppm.

IR (KBr) 3230 (br), 1620 (br), 1500 (br), 1430, 730, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity) 288 (M^++1 , 64), 287 (M^+ , 2), 230 (28), 229 (100), 153 (46).

Elemental analysis

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1 Preparation of Functionalized α -Heteroaloin Substituted Amino Acids. General Procedure.

5 A BBr_3 solution (1 M in CH_2Cl_2 , 1.1 equiv) was added to a solution of
2-acetamido-N-benzyl-2-ethoxyacetamide (1 equiv) in CH_2Cl_2 (10 mmol/125 mL).
The mixture was stirred at room temperature (5 h) and then concentrated to
dryness in vacuo to give 2-acetamido-N-benzyl-2-bromoacetamide as a pale yellow
crystalline material. The bromo adduct was then dissolved in THF (10 mmol/250
10 mL), cooled (-78 °C), and then added over a 15 min interval to a cooled (-78 °C)
solution of the heteroatom nucleophile in THF (1 mmol/1 mL). The reaction
mixture was stirred at this temperature (30 min) and then at room temperature
15 (90 min). The insoluble salts were filtered and the filtrate concentrated in vacuo.
The residue was then purified by flash column chromatography on SiO_2 gel using
the indicated solvent as the eluent.

Using this procedure the following examples were
prepared.

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EXAMPLE 54

1 Synthesis of 2-Acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide.

By making use of 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 minol), BBr_3 (1 M in CH_2Cl_2 , 13.2 mL, 13.2 mmol), and Me_2NH (5-6 equiv) was obtained a brown residue which was purified by flash column chromatography on SiO_2 gel (2.5% $\text{MeOH}/\text{CHCl}_3$) to give the desired product. The product was recrystallized from ethyl acetate/hexane to give light yellow cubic crystals.

Yield: 1.20 g (40%).

1.0 R_f 0.39 (5% $\text{MeOH}/\text{CHCl}_3$).

mp 104-106 °C.

15 ^1H NMR (DMSO-d_6) δ 1.91 (s, 3 H), 2.11 (s, 6 H), 4.22 (dd, $J = 5.2, 14.7$ Hz, 1 H), 4.34 (dd, $J = 6.1, 14.7$ Hz, 1 H), 5.11 (d, $J = 8.3$ Hz, 1 H), 7.23-7.31 (m, 5 H), 8.18 (d, $J = 8.3$ Hz, 1 H), 8.55 (br s, 1 H).

13C NMR (DMSO-d_6) 22.43, 40.33 (2 C), 42.28, 69.42, 126.73, 127.27 (2 C), 128.21(2 C), 139.49, 168.49, 170.31 ppm.

20 IR (KBr) 3280, 1670 (br), 1500 (br), 1460, 760, 700 cm^{-1} .

Mass spectrum (FD) 250 ($M^{++}1$).

Elemental analysis

Calculated for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_2$ 62.63% C; 7.68% H; 16.85% N.

25 Found 62.82% C; 7.66% H; 16.69% N.

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EXAMPLE 55

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), BBr₃ (1 M in CH₂Cl₂, 8.8 mL, 8.8 mmol), and anhydrous NH₂OH (5-6 equiv) gave an oily residue. The residue was separated into three components by flash chromatography on SiO₂ gel (7.5% MeOH/CHCl₃).

2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.14 g (7%).

10 R_f 0.30 (8% MeOH/CHCl₃).

mp 144-146 °C (dec.) (recrystallized from EtOH)

15 ¹H NMR (DMSO-d₆) δ 1.88 (s, 3 H), 4.31 (d, J = 5.7 Hz, 2 H), 5.08 (dd, J = 4.4, 8.1 Hz, 1 H), 5.94 (dd, J = 2.8, 4.4 Hz, 1 H), 7.19-7.35 (m, 5 H), 7.52 (d, J = 2.8 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 1 H), 8.42 (t, J = 5.7 Hz, 1 H).

20 ¹³C NMR (DMSO-d₆) 22.69, 42.25, 67.86, 126.69, 127.14 (2 C), 128.18 (2 C), 139.08, 168.53, 169.67 ppm.

25 IR (KBr) 3320 (br), 1660 (br), 1540 (br), 1460, 750, 700 cm⁻¹.

Mass spectrum (FD) 238 (M⁺⁺ 1).

Elemental analysis

Calculated for C₁₁H₁₅N₃O₃ 55.69% C; 6.37% H; 17.71% N.

25 Found 55.86% C; 6.37% H; 17.38% N.

Dimer A.

Yield: 0.05 g (3%).

R_f 0.27 (8% MeOH/CHCl₃).

30 mp 177-179 °C (recrystallized from EtOH).

¹H NMR (DMSO-d₆) δ 1.82 (s, 6 H), 4.25-4.34 (m, 4 H), 5.21 (d, J = 9.3 Hz, 2 H), 7.20-7.33 (m, 10 H), 8.16 (d, J = 9.3 Hz, 2 H), 8.26 (t, J = 5.8 Hz, 2 H), 8.51 (s, 1 H).

35 ¹³C NMR (DMSO-d₆) 22.54 (2 C), 42.30 (2 C), 67.55 (2 C), 126.63 (2 C), 127.13 (4 C), 128.11 (4 C), 139.02 (2 C), 168.24 (2 C), 169.33 (2 C) ppm.

IR (KBr) 3240 (br), 1640 (br), 1510 (br), 1450, 690 cm⁻¹.

Mass spectrum (FD) 442 (M⁺⁺ 1).

109

1 Elemental analysis

Calculated for C₂₂H₂₇N₅O₅ 59.85% C; 6.16% H; 15.86% N.

Found 59.59% C; 6.08% H; 15.64% N.

5 Dimer B.

Yield: 0.10 g (6%).

R_f 0.18 (8% MeOH/CHCl₃).

mp 184-186 °C (recrystallized from MeOH).

10 ¹H NMR (DMSO-d₆) δ 1.87 (6 H), 4.20 (dd, J = 5.3, 15.3 Hz, 2 H), 4.44 (dd, J = 6.2, 15.3 Hz, 2 H), 5.28 (d, J = 9.0 Hz, 2 H), 7.15-7.31 (m, 10 H), 8.00 (d, J = 9.0 Hz, 2 H), 8.39 (dd, J = 5.3, 6.2 Hz, 2 H), 8.51 (s, 1 H).

15 ¹³C NMR (DMSO-d₆) 22.50 (2 C), 42.58 (2 C), 69.98 (2 C), 126.73 (2 C), 127.23 (4 C), 128.22 (4 C), 139.08 (2 C), 167.60 (2 C), 169.57 (2 C) ppm.

IR (KBr) 3300 (br), 1660 (br), 1530 (br), 1450, 740, 700 cm⁻¹.

Mass spectrum (FD) 442 (M⁺⁺1).

20 Elemental analysis

Calculated for C₂₂H₂₇N₅O₅ 59.85% C; 6.16% H; 15.86% N.

Found 60.09% C; 5.93% H; 15.76% N.

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EXAMPLE 56

1 Improved Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

2-Acetamido-N-benzyl-2-bromoacetamide (prepared from 2-

acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol) and BBr_3 (1 M in

5 CH_2Cl_2 , 17.2 mL, 17.2 mmol)) was dissolved in THF (250 mL), cooled (-10 °C), and
then added dropwise (30 min) to a suspension of NH_2OH (5-6 equiv) in TlIF (50
mL) at -10 °C. The reaction mixture was stirred (30 min) at this temperature and
then allowed to warm to room temperature (1 h). The insoluble materials were
10 filtered and the filtrate was concentrated in vacuo. The residue was separated
into two components by flash column chromatography on SiO_2 gel (7.5%
MeOH/CHCl₃).

15 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.66 g (23%).

mp 144-146 °C (dec.) (recrystallized from EtOH).

Dimer B.

20 Yield: 0.10 g (5%).

mp 184-186 °C (recrystallized from MeOH).

Dimer A was not observed under these conditions.

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EXAMPLE 57

1 Synthesis of 2-Acetamido-N-benzyl-2-(N²-phenylhydrazino)acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol),

BBR₃ (1 M in CH₂Cl₂, 10.0 mL, 10.0 mmol), and phenylhydrazine (2.60 g, 24.0

5 mmol) gave a pale yellow oily residue which was purified by flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give the desired product. The product was recrystallized from chloroform/hexane as a light yellow solid.

Yield: 0.75 g (29%).

10 R_f 0.26 (2% MeOH/CHCl₃).

mp 132-134 °C.

15 ¹H NMR (DMSO-d₆) δ 1.89 (s, 3 H), 4.28 (d, J = 5.8 Hz, 2 H), 4.89 (d, J = 5.2 Hz, 1 H), 5.09 (dd, J = 5.2, 7.4 Hz, 1 H), 6.61 (t, J = 7.4 Hz, 1 H), 6.70-7.28 (m, 10 H), 8.29 (d, J = 7.4 Hz, 1 H), 8.60 (t, J = 5.8 Hz, 1 H).

15 ¹³C NMR (DMSO-d₆) 22.88, 42.22, 66.22, 112.66 (2 C), 117.57, 126.65, 127.08 (2 C), 128.15 (2 C), 128.53 (2 C), 139.12, 149.90, 168.66, 170.04 ppm.

20 IR (KBr) 3300, 1640 (br), 1610, 1520 (br), 1460, 760, 700 cm⁻¹.

Mass spectra (FD) 313 (M⁺⁺¹).

Elemental analysis

Calculated for C₁₇H₂₀N₄O₂ 65.37% C; 6.45% H; 17.94% N.

25 Found 65.15% C; 6.25% H; 17.71% N.

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EXAMPLE 58

1 Synthesis of 2-Acetamido-N-benzyl-2-(N²-benzyloxycarbonylhydrazino)acetamide.

Employing 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr₃ (1 M in CH₂Cl₂, 15.0 mL, 15.0 mmol), and benzyl carbazate (4.58 g, 27.6 mmol), 0.95 g (21%) of the desired product was obtained. The product was recrystallized from chloroform/hexane to give a white amorphous solid.
R_f 0.32 (2% MeOH/CHCl₃).

mp 152-154 °C.

10 ¹H NMR (DMSO-d₆) δ 1.85 (s, 3 H), 4.27 (d, J = 4.4 Hz, 2 H), 5.00 (s, 2 H), 5.14 (dd, J = 3.1, 8.0 Hz, 1 H), 5.23 (t, J = 3.1 Hz, 1 H), 7.25-7.35 (m, 10 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.56 (br s, 1 H), 8.66 (br s, 1 H).

15 ¹³C NMR (DMSO-d₆) 22.71, 42.23, 65.56, 65.97, 126.69, 127.16 (2 C), 127.61 (2 C), 127.77, 128.13 (2 C), 128.27 (2 C), 136.74, 138.87, 168.04, 169.95 ppm.

IR (KBr) 3325, 1620 (br), 1500 (br), 1440, 740, 680 cm⁻¹.

Mass spectrum (FD) 371 (M⁺⁺ 1).

20 Elemental analysis

Calculated for C₁₉H₂₂N₄O₄ 61.61% C; 5.99% H; 15.13% N.

Found 61.40% C; 6.21% H; 15.39% N.

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EXAMPLE 59

1 Synthesis of 2-Acetamido-N-benzyl-2-phenoxyacetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr₃ (1 M in CH₂Cl₂, 15.0 mL, 15.0 mmol), and NaOPh (4.18 g, 30 mmol) gave a brown oily residue which was purified by flash column chromatography on SiO₂ gel using first CHCl₃ and then 2% MeOH/CHCl₃ as the eluents to give the desired product. The compound was recrystallized from chloroform/hexane.

Yield: 0.80 g (22%).

10 R_f 0.58 (3% MeOH/CHCl₃).

mp 125-128 °C (softens at 122 °C).

15 ¹H NMR (DMSO-d₆) δ 1.83 (s, 3 H), 4.35 (d, J = 5.7 Hz, 2 H), 6.18 (d, J = 9.4 Hz, 1 H), 6.94-6.99 (m, 2 H), 7.02-7.33 (m, 8 H), 8.98 (t, J = 5.7 Hz, 1 H), 9.10 (d, J = 9.4 Hz, 1 H).

20 ¹³C NMR (DMSO-d₆) 22.54, 42.24, 76.44, 116.09 (2 C), 121.78, 126.84, 127.26 (2 C), 128.25 (2 C), 128.44 (2 C), 138.84, 155.97, 166.63, 170.73 ppm.

25 IR (KBr) 3300, 1650 (br), 1600, 1530 (br), 1490, 1450, 760, 700 cm⁻¹.

Mass spectrum (FD) 299 (M⁺⁺¹).

Elemental analysis

Calculated for C₁₇H₁₈N₂O₃·0.5 H₂O 66.43% C; 6.23% H; 9.11% N.

25 Found 66.62% C; 6.23% H; 9.16% N.

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EXAMPLE 60

1 Synthesis of 2-Acetamido-N-benzyl-2-(methylmercapto)acetamide.

A cooled (-78 °C) solution of Et₃N (4.85 g, 48.0 mmol) in THF (20 mL) was added to a cooled (-78 °C) solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and BBr₃ (1 M in CH₂Cl₂, 20.0 mL, 20.0 mmol)) in THF (275 mL). A cooled (-78 °C) solution of excess MeSH (5.6 equiv) in THF (55 mL) was then added. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (1 h). The insoluble materials were filtered and the filtrate was evaporated to dryness in vacuo. The oily residue obtained was purified by flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give 1.10 g (27%) of the desired product as a yellow orange oil. The product was purified by a second flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give 0.72 g of the pure product as a white solid.

R_f 0.65 (3% MeOH/CHCl₃).

mp 155-157 °C.

¹H NMR (CD₃NO₂) δ 1.98 (s, 3 H), 2.08 (s, 3 H), 4.39 (dd, J = 6.1, 15.2 Hz, 1 H), 4.49 (dd, J = 6.1, 15.2 Hz, 1 H), 5.51 (d, J = 7.8 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.17-7.41 (m, 6 H)

25 ^{13}C NMR (CD_3NO_2) 12.28, 22.94, 44.26, 56.03, 128.46, 128.60 (2 C), 129.77 (2 C),
140.17, 169.19, 171.06 ppm.

IR (KBr) 3320, 1650 (br), 1520 (br), 1460, 750 cm⁻¹

Mass spectrum (FD) 253 (M^{++})

30 Elemental analysis

Calculated for C₁₂H₁₆N₂O₂S: 57.12% C; 6.20% H; 11.13% N

Found 57.06% C; 6.57% H; 11.28% N

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EXAMPLE 61

- 1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide.**

Using the procedure described for the synthesis of 2-acetamido-N-benzyl-2-(methylmercapto)acetamide, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and EtSH (0.65 g, 10.4 mmol) were converted to 0.80 g (38%) of the desired product. The compound was further purified by recrystallization from chloroform/hexane to give a beige solid.

R_f 0.60 (4% MeOH/CHCl₃)

mp 146-148 °C

¹H NMR (DMSO-d₆) δ 1.56 (t, J = 7.4 Hz, 3 H), 1.88 (s, 3 H), 2.49-2.67 (m, 2 H), 4.23 (dd, J = 5.9, 15.2 Hz, 1 H), 4.32 (dd, J = 5.9, 15.2 Hz, 1 H), 5.55 (d, J = 9.1 Hz, 1 H), 7.20-7.35 (m, 5 H), 8.59 (d, J = 9.1 Hz, 1 H). 8.75 (s, 1 H).

¹³C NMR (DMSO-d₆) 14.73, 22.43, 23.73, 42.10, 53.70, 126.87, 127.14 (2 C), 128.32 (2 C), 139.01, 167.89, 169.02 ppm.

IR (KBr) 3240, 1620 (br), 1510 (br), 1415, 680, 640 cm^{-1}

Mass spectrum (FD) 267 ($M^{++}+1$)

Elemental analysis

Calculated for C₁₃H₁₈N₂O₂S·0.25 H₂O 57.65% C; 6.88% H; 10.34% N

Found 57.48% C; 6.84% H; 10.28% N.

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1 Preparation of Functionalized α -Heteroatom Substituted Amino Acids. General Procedure.

5 A mixture of 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (1 equiv), and the nitrogen nucleophile (4-5 equiv) in MeOH (1 mmol/1 mL) was stirred at 55-60 °C (3 h). The solvent was removed in vacuo and the residue was purified by flash column chromatography on SiO₂ gel using the indicated solvents as the eluent.

10 Using this procedure the following examples were prepared.

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EXAMPLE 62

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-methoxyamino)acetamide.

Using a MeOH solution of MeONH₂ (prepared from MeONH₂·HCl (2.83 g, 33.9 mmol) and NaOMe (1.41 g, 26.1 mmol)), and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.70 g, 7.67 mmol) gave an oily residue which was purified by flash column chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give the desired product. The product was recrystallized from chloroform/hexane.

10 Yield: 0.80 g (42%).

R_f 0.23 (2% MeOH/CHCl₃)

mp 95-97 °C.

15 ¹H NMR (DMSO-d₆) δ 1.88 (s, 3 H), 3.38 (s, 3 H), 4.22-4.41 (m, 2 H), 5.18 (dd, J = 4.9, 7.8 Hz, 1 H), 6.78 (d, J = 4.9 Hz, 1 H), 7.21-7.32 (m, 5 H), 8.33 (d, J = 7.8 Hz, 1 H), 8.56 (br s, 1 H).

20 ¹³C NMR (DMSO-d₆) 22.64, 42.28, 61.42, 66.25, 126.74, 127.19 (2 C), 128.19 (2 C), 139.11, 167.95, 169.66 ppm.

IR (KBr) 3300, 1650, 1620, 1510 (br), 1440, 750, 680 cm⁻¹.

Mass spectrum (FD) 252 (M⁺⁺1).

Elemental analysis

25	Calculated for C ₁₂ H ₁₇ N ₃ O ₃	57.63% C; 6.82% H; 16.72% N.
	Found	57.06% C; 6.63% H; 16.65% N.

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EXAMPLE 63

- Synthesis of 2-Acetamido-N-benzyl-2-(N-(N-methylhydroxymino))acetamide.

An MeOH solution (30 mL) of MeNHOH (21.74 mmol) (prepared from MeNHOH·HCl (2.36 g, 28.26 mmol) and NaOMe (1.17 g, 21.74 mmol)) and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.20 g, 6.25 mmol) gave a residue which was purified by flash column chromatography on SiO₂ gel (6% MeOH/CHCl₃) to give the desired product as a white solid. The product was then purified by recrystallization from EtOH.
Yield: 0.95 g (61%).

R_f 0.32 (8% MeOH/CHCl₃).
mp 159-161 °C.

¹H NMR (DMSO-d₆) δ 1.95 (s, 3 H), 2.43 (s, 3 H), 4.26 (dd, J = 5.7, 15.1 Hz, 1 H), 4.35 (dd, J = 5.7, 15.1 Hz, 1 H), 5.09 (d, J = 9.1 Hz, 1 H), 7.21-7.29 (m, 5 H), 8.05 (s, 1 H), 8.18 (d, J = 9.1 Hz, 1 H), 8.23 (t, J = 5.7 Hz, 1 H).

¹³C NMR (DMSO-d₆) 22.40, 42.34, 43.92, 71.49, 126.62, 127.12 (2 C), 128.12 (2 C), 139.14, 167.82, 170.28 ppm.

IR (KBr) 3440 (br), 3300, 1640, 1530, 1460, 750, 700 cm⁻¹.

Mass spectrum (FD) 252 (M⁺⁺1).

Elemental analysis

Calculated for C ₁₂ H ₁₇ N ₃ O ₃	57.36% C; 6.82% H; 16.72% N.
Found	57.65% C; 6.59% H; 16.66% N.

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EXAMPLE 64

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-(N,O-dimethylhydroxyamino))acetamide.

An MeOH solution (20 mL) of MeNHOMe (17.39 mmol) (prepared from MeNHOMe-HCl (2.20 g, 23.02 mmol) and NaOMe (0.94 g, 17.39 mmol)) and 2.5 acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.10 g, 5.97 mmol) gave a solid residue. Flash column chromatography of the solid on SiO₂ gel (2% MeOH/CHCl₃) yielded pure desired product. The product was recrystallized from EtOH.

10 Yield: 1.30 g (82%).

R_f 0.39 (2% MeOH/CHCl₃).

mp 165-167 °C.

15 ¹H NMR (DMSO-d₆) δ 1.93 (s, 3 H), 2.43 (s, 3 H), 3.32 (s, 3 H), 4.25 (dd, J = 5.9, 14.9 Hz, 1 H), 4.37 (dd, J = 5.9, 14.9 Hz, 1 H), 5.19 (d, J = 9.4 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.31 (d, J = 9.4 Hz, 1 H), 8.56 (t, J = 5.9 Hz, 1 H).

20 ¹³C NMR (DMSO-d₆) 22.36, 39.68, 42.34, 59.16, 70.33, 126.74, 127.41 (2 C), 128.21 (2 C), 139.30, 167.38, 170.30 ppm.

IR (KBr) 3300, 1640 (br), 1540 (br), 1460, 750, 700 cm⁻¹.

Mass spectrum (FD) 266 (M⁺⁺1).

Elemental analysis

25 Calculated for C₁₃H₁₉N₃O₃ 58.85% C; 7.22% H; 15.84% N.

Found 59.05% C; 7.37% H; 15.75% N.

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EXAMPLE 65

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-isoxazolidino)acetamide.

Using 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (1.60 g, 4.55 mmol), isoxazolidine (prepared from isoxazolidine hydrobromide (2.41 g, 15.65 mmol) and NaOMe (0.70 g, 13.04 mmol)) gave the desired product. The product was recrystallized from chloroform/hexane to give a white amorphous solid.

Yield: 0.80 g (64%)

10 R_f 0.29 (4% MeOH/CHCl₃).

mp 149-151 °C.

¹H NMR (DMSO-d₆) δ 1.91 (s, 3 H), 2.05-2.20 (m, 2 H), 2.45-2.89 (m, 1 H), 2.98-3.07 (m, 1 H), 3.74-3.90 (m, 2 H), 4.25 (dd, J= 6.1, 15.3 Hz, 1 H), 4.35 (dd, J= 6.1, 15.3 Hz, 1 H), 5.23 (d, J= 9.2 Hz, 1 H), 7.15-7.35 (m, 5 H), 8.49 (d, J= 9.2 Hz, 1 H), 8.56 (br s, 1 H).

¹³C NMR (DMSO-d₆) 22.26, 28.26, 42.15, 48.94, 66.19, 68.77, 126.64, 127.02 (2 C), 128.13 (2 C), 139.22, 167.43, 170.27 ppm.

IR (KBr) 3400 (br), 3300, 1650, 1530, 1470, 740, 700, 610 cm⁻¹.
 Mass spec. (ESI)

Mass spectrum (FD) 278 ($M^{++}1$).

Elemental analysis

25	Calculated for C ₁₄ H ₁₉ N ₃ O ₃	60.64% C; 6.91% H; 15.15% N.
	Found	60.16% C; 7.04% H; 15.07% N.

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1 Preparation of Functionalized α -Heteroatom Substituted Amino Acids. General Procedure.

2-Acetamido-N-benzyl-2-ethoxyacetamide (1 equiv) was suspended in
5 Et₂O (100 mL/10 mmol), and then BF₃·Et₂O (1.6-2.4 equiv) was rapidly added and
the resulting solution was stirred (10 min). The nucleophile (H₂O or EtSH) (1.6-4.0
equiv) was then added and the reaction was stirred at room temperature (18-48 h).
10 The reaction was then quenched by the addition of an aqueous NaHCO₃ (100
mL/10 mmol)/ice mixture. The experimental workup varied slightly for each
compound and is described in the following examples along with
the observed spectral properties.

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EXAMPLE 661 Synthesis of 2-Acetamido-N-benzyl-2-hydroxyacetamide.

Reacting 2-acetamido-N-benzyl-2-ethoxyacetamide (1.00 g, 4.0 mmol), BF₃·Et₂O (0.91 g, 6.4 mmol) and H₂O (0.12 g, 6.7 mmol) followed by aqueous 5 NaHCO₃ workup gave an aqueous reaction mixture. The solution was then extracted with EtOAc (3 X 50 mL), and the combined EtOAc extracts were dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column 10 chromatography on SiO₂ gel (3% MeOH/CHCl₃) to give the desired product as a white solid.

Yield: 0.30 g (34%).

R_f 0.14 (3% MeOH/CHCl₃).

mp 136-138 °C.

15 ¹H NMR (DMSO-d₆) δ 1.85 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.48 (dd, J = 5.5, 8.6 Hz, 1 H), 6.47 (d, J = 5.5 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.52 (t, J = 5.9 Hz, 1 H), 8.59 (d, J = 8.6 Hz, 1 H).

20 ¹³C NMR (DMSO-d₆) 22.66, 41.99, 71.42, 126.66, 127.22 (2 C), 128.13 (2 C), 139.20, 169.47, 169.62 ppm.

IR (KBr) 3300, 1620, 1530 (br), 1430 (br), 730, 690 cm⁻¹.

Mass spectrum, m/e (relative intensity) 223 (M⁺+1, 1), 163 (11), 134 (9), 106 (46), 91 (25) (100), 77 (22), 65 (38).

Elemental analysis

Calculated for C₁₁H₁₄N₂O₃ 59.45% C; 6.35% H; 12.61% N.

Found 59.24% C; 6.36% H; 12.50% N.

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EXAMPLE 67

1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide.

5 Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol),
BF₃·Et₂O (2.72 g, 19.2 mmol) and EtSH (2.38 g, 38.4 mmol) gave an aqueous
reaction mixture. The solution was extracted with CHCl₃ (3 x 100 mL). The
combined CHCl₃ layers were dried (Na₂SO₄), and then concentrated in vacuo to
give the desired product as white solid.

10 Yield: 1.90 g (89%).

15 R_f 0.60 (4% MeOH/CHCl₃).

20 mp 148-149 °C (mixed melting point with an authentic sample of Example 61
was undepressed).

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EXAMPLE 68

1 Synthesis of 2,2-Diacetamido-N-benzylacetamide.

5 Ac₂O (1 mL) was added to a solution of 2-acetamido-N-benzyl-2-aminoacetamide (1.10 g, 4.98 mmol) in dry pyridine (10 mL) and then CH₂Cl₂ (20 mL) was added. The mixture was stirred at room temperature (4 h) and then the volatile materials were removed in vacuo. The residue was then treated with a saturated aqueous NaHCO₃ solution (50 mL). The white solid that remained was the desired product and was filtered, dried (Na₂SO₄), and recrystallized from MeOH.

10 Yield: 1.20 g (92%).

15 mp 265-267 °C (dec.).

1H NMR (DMSO-d₆) δ 1.84 (s, 6 H), 4.26 (d, J = 5.8 Hz, 2 H), 5.71 (t, J = 7.6 Hz, 1 H), 7.20-7.31 (m, 5 H), 8.44 (d, J = 7.6 Hz, 2 H), 8.48 (t, J = 5.8 Hz, 1 H).

13C (DMSO-d₆) 22.44 (2 C), 42.26, 56.99, 126.62, 127.02 (2 C), 128.12 (2 C), 139.15, 168.19, 169.39 (2 C) ppm.

20 IR (KBr) 3260, 1530, 1500, 740, 690 cm⁻¹.

Mass spectrum (FD) 264 (M⁺⁺1).

Elemental analysis

Calculated for C ₁₃ H ₁₇ N ₃ O ₃	59.30% C; 6.51% H; 15.96% N.
Found	59.16% C; 6.49% H; 15.86% N.

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EXAMPLE 69

1 Synthesis of 2-Acetamido-N-benzyl-2-trifluoroacetamidoacetamide.

5 Ice cold trifluoroacetic anhydride (8 mL) was added in one portion to
ice cold 2-acetamido-N-benzyl-2-aminoacetamide (1.00 g, 4.53 mmol). The
reaction was accompanied by the evolution of heat. After stirring (5 min), the
volatile materials were removed in vacuo. The residue was treated with a
saturated aqueous NaHCO₃ solution (20 mL), and the solid that remained was
10 filtered and washed with H₂O to give the desired product. The product was
recrystallized from EtOH.

Yield: 1.00 g (70%).

R_f 0.34 (8% MeOH/CHCl₃).

15 mp 228-230 °C.

20 ¹H NMR (DMSO-d₆) δ 1.90 (s, 3 H), 4.30 (d, J = 5.1 Hz, 2 H), 5.85 (d, J = 8.0 Hz, 1 H),
7.21-7.35 (m, 5 H), 8.64 (d, J = 8.0 Hz, 1 H), 8.75 (t, J = 5.1 Hz, 1 H), 10.04 (s, 1
H).

25 ¹³C NMR (DMSO-d₆) 22.52, 42.52, 57.42, 117.4 (q, JCF = 288.3 Hz), 126.80, 127.16 (2
C), 128.21 (2 C), 138.93, 156.14 (q, JCF = 35.3 Hz), 166.39, 169.88 ppm.
IR (KBr) 3300, 1720, 1660, 1520, 1380, 760, 700 cm⁻¹.

30 Mass spectrum (FD) 318 (M⁺⁺ 1).

25 Elemental analysis

Calculated for C₁₃H₁₄N₃O₃F₃ 49.21% C; 4.45% H; 13.24% N.

Found 49.48% C; 4.43% H; 13.10% N.

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EXAMPLE 70

1 Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide Tetrafluoroborate.

5 A solution of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitro-methane (6 mL). The reaction mixture was stirred at this temperature (15 min) and then at room temperature (2 h). Anhydrous Et₂O (~50 mL) was added to the 10 reaction mixture and the white solid that separated was filtered, washed with Et₂O, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171-173 °C (dec.).

15 ¹H NMR (CD₃NO₂) δ 2.14 (s, 3 H), 3.18 (s, 9 H), 4.50 (d, J = 5.8 Hz, 2 H), 5.70 (d, J = 9.3 Hz, 1 H), 7.30-7.41 (m, 5 H), 7.57 (d, J = 9.3 Hz, 1 H), 7.70 (br s, 1 H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm⁻¹.

20 Mass spectrum (FD) 264 (M⁺).

Elemental analysis

Calculated for C₁₄H₂₂N₃O₂BF₄ 47.89% C; 6.31% H; 11.97% N.

Found 47.80% C; 6.33% H; 12.00% N.

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EXAMPLE 71

- ## 1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide.

A solution of *m*-chloroperbenzoic acid (1.00 g (~65%), 3.76 mmol) in CH₂Cl₂ (10 mL) was added dropwise into a stirred, cooled (-10 to -15 °C) CH₂Cl₂ solution (125 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (1.00 g, 3.76 mmol) under N₂. The reaction was stirred (30 min) at this temperature and then the *m*-chlorobenzoic acid was precipitated as its ammonium salt by passing NH₃ gas over the surface of the reaction solution. The excess NH₃ was removed by passing N₂ gas through the solution (20 min) at room temperature. The ammonium salt was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on SiO₂ gel (2% MeOH/CHCl₃) to give the desired product. The product was recrystallized from chloroform/hexane as a white granular solid.

Yield: 0.55 g (52%).

R_f 0.23 (2% MeOH/CHCl₃).

20 mp 135-137 °C.

¹H NMR (DMSO-d₆) δ 1.15 (t, J = 7.5 Hz, 3 H), 1.99 (s, 3 H), 2.49-2.56 (m, 1 H), 2.65-2.72 (m, 1 H), 4.34 (d, J = 5.7 Hz, 2 H), 5.55 (d, J = 9.5 Hz, 1 H), 7.23-7.34 (m, 5 H), 8.74 (d, J = 9.5 Hz, 1 H), 8.77 (t, J = 5.7 Hz, 1 H).

25. ^{13}C NMR (DMSO- d_6) 7.03, 22.34, 42.40, 42.47, 67.15, 126.89, 127.27 (2 C), 128.24 (2 C), 138.55, 164.66, 170.18 ppm.

IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm⁻¹

Mass spectrum (FD) 283 ($M^{++}1$)

30 Elemental analysis

Calculated for C₁₃H₁₈N₂O₃S 55.30% C; 6.43% H; 9.99% N;

Found 55.17% C; 6.38% H; 9.70% N.

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EXAMPLE 72

1 Synthesis of 2-Acetamido-N-benzyl-2-(S-ethylmercapto)acetamide-S-oxide.

A solution of NaIO₄ (1.77 g, 8.27 mmol) in H₂O (20 mL) was added dropwise into a stirred solution of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (2.00 g, 7.52 mmol) in MeOH (25 mL). A precipitate appeared rapidly. H₂O (~30 mL) was added to the mixture to dissolve most of the suspension, and the reaction was stirred (4 h) at room temperature. The reaction was concentrated in vacuo and the remaining aqueous mixture was extracted with CHCl₃ (3 x 100 mL). The combined CHCl₃ extracts were dried (Na₂SO₄) and the solvent was removed in vacuo. The oily residue (1.95 g, 92%) solidified on drying in vacuo. NMR analysis (DMSO-d₆) of the product showed that it was a 2:1 mixture of the two diastereomers of the desired product. The reaction was recrystallized from EtOAc to give nearly pure diastereomer A (1.20 g) that was obtained from the m-chloroperbenzoic acid reaction. The EtOAc mother liquor was concentrated and the remaining residue (0.75 g) was recrystallized from ethyl acetate/hexane to give a diastereomeric mixture (0.41 g) of the two diastereomers A and B in a 2:3 ratio, respectively.

R_f 0.60 (4% MeOH/CHCl₃).

mp 135-137 °C (softens at 117 °C).

25 IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm⁻¹.
Mass spectrum (FD) 283 (M⁺⁺1).

Elemental analysis: Calculated for C₁₃H₁₈N₂O₃S: 55.30% C; 6.43% H; 9.92% N.
Found: 55.58% C; 6.49% H; 9.97% N.

30 The following NMR spectral properties have been assigned to compounds A and B.

Diastereomer A.

35 ¹H NMR (DMSO-d₆) δ 1.16 (t, J = 7.5 Hz, 3 H), 2.00 (s, 3 H), 2.49-2.72 (m, 2 H), 4.28-4.39 (m, 2 H), 5.56 (d, J = 9.7 Hz, 1 H), 7.21-7.34 (m, 5 H), 8.71-8.77 (m, 2 H).

¹³C NMR (DMSO-d₆) 7.10, 22.43, 42.48, 42.57, 67.23, 126.98, 127.36 (2 C), 128.33 (2 C), 138.63, 164.73, 170.25 ppm.

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1 Diastercomer B.

1H NMR (DMSO-d₆) δ 1.13 (t, J = 7.6 Hz, 3 H), 1.94 (s, 3 H), 2.49-2.72 (m, 2 H), 4.28-4.39 (m, 2 H), 5.71 (d, J = 9.9 Hz, 1 H), 7.21-7.34 (m, 5 H), 8.83 (d, J = 9.9 Hz, 1 H), 8.98 (t, J = 5.6 Hz, 1 H).

5 13C NMR (DMSO-d₆) 6.47, 22.43, 41.53, 42.55, 67.90, 126.98, 127.36 (2 C), 128.33 (2 C), 138.39, 164.43, 169.82 ppm.

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EXAMPLE 73

1 Synthesis of 2-Acetamido-N-benzyl-2-(ethanesulfonyl)acetamide.

An aqueous solution (20 mL) of NaIO₄ (3.00 g, 14.02 mmol) was added to a MeOH solution (20 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (0.95 g, 3.57 mmol). The initial homogeneous solution rapidly became turbid. H₂O (~10 mL) was then added dropwise until the system became homogeneous. The solution was stirred (18 h) at 50-60 °C. MeOH (50 mL) was added to the reaction solution and the precipitated salt was filtered and washed with MeOH (10 mL). The filtrate was concentrated and the remaining solution was extracted with CHCl₃ (3 x 50 mL). The combined CHCl₃ extracts were dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash chromatography on SiO₂ gel (1% MeOH/CHCl₃) to give the desired product. The product was further purified by recrystallization from EtOH.

Yield: 0.34 g (32%).

R_f 0.34 (3% MeOH/CHCl₃).

mp 161-163 °C.

¹H NMR (DMSO-d₆) δ 1.22 (t, J = 7.4 Hz, 3 H), 1.99 (s, 3 H), 3.04-3.24 (m, 2 H), 4.31 (dd, J = 5.7, 15.3 Hz, 1 H), 4.41 (dd, J = 5.7, 15.3 Hz, 1 H), 5.93 (d, J = 9.8 Hz, 1 H), 7.22-7.35 (m, 5 H), 9.13 (t, J = 5.7 Hz, 1 H), 9.17 (d, J = 9.8 Hz, 1 H).

¹³C NMR (DMSO-d₆) 5.72, 22.27, 42.63, 45.43, 69.14, 127.02, 127.28 (2 C), 128.33 (2 C), 138.16, 161.88, 169.83 ppm.

IR (KBr) 3300, 2940, 1660, 1520, 1310, 1230, 1120, 900 cm⁻¹.

Mass spectrum (FD) 298 (M⁺). -

30 Elemental analysis

Calculated for C₁₃H₁₈N₂O₄S: 52.33% C; 6.08% H; 9.39% N

Found 52.52% C: 6.06% H: 9.53% N.

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EXAMPLE 74

1 Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide Tetrafluoroborate.

5 A solution of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitro-methane (6 mL). The reaction mixture was stirred at this temperature (15 min) and then at room temperature (2 h). Anhydrous Et₂O (~50 mL) was added to the 10 reaction mixture and the white solid that separated was filtered, washed with Et₂O, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171-173 °C (dec.).

15 ¹H NMR (CD₃NO₂) δ 2.14 (s, 3 H), 3.18 (s, 9 H), 4.50 (d, J = 5.8 Hz, 2 H), 5.70 (d, J = 9.3 Hz, 1 H), 7.30-7.41 (m, 5 H), 7.57 (d, J = 9.3 Hz, 1 H), 7.70 (br s, 1 H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm⁻¹.

20 Mass spectrum (FD) 264 (M⁺).

Elemental analysis

Calculated for C₁₄H₂₂N₃O₂BF₄ 47.89% C; 6.31% H; 11.97% N.

Found 47.80% C; 6.33% H; 12.00% N.

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Example 75

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole)acetamide.* A solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr_3 (1 M CH_2Cl_2 solution, 8.8 mL, 8.8 mmol)) was prepared in THF (225 mL) and cooled to -78 °C. It was then added under N_2 gas atmosphere to a cooled (-78 °C) suspension of potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was stirred at -78 °C (1 h) and then at room temperature (1 h). It was then treated with water (10 mL) and acidified with 5% citric acid to pH 4.0 after which it was made basic with aqueous saturated Na_2CO_3 solution. The aqueous mixture was extracted with EtOAc (2 x 250 mL) and the organic layers were dried (Na_2SO_4). The volatile materials were removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using 3% MeOH/CHCl₃ as the eluant to give 0.4 g (18%) of the desired product. It was purified by recrystallization from EtOH: mp 182-184 °C; R_f 0.44 (4% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.91 (s, COCH₃), 4.30 (d, J = 5.5 Hz, CH₂), 6.01 (s, 2 x C₃H), 6.38 (d, J = 8.7 Hz, CH), 6.85 (s, 2 x C₂H), 7.11-7.35 (m, 5PhH), 8.96 (t, J = 5.5 Hz, NH), 9.14 (d, J = 8.7 Hz, NH); ¹³C NMR (DMSO-d₆) 22.22 (COCH₃), 42.15 (CH₂), 62.86 (CH), 107.79 (2C₃), 119.19 (2C₂), 126.76 (C_{4'}), 127.01 (2C_{2'} or 2C_{3'}), 128.11 (2C_{2'} or 2C_{3'}), 138.34 (C_{1'}), 166.37 (CONH), 169.41 (COCH₃) ppm; mass spectrum, m/e (relative intensity) 272 (M⁺⁺¹, 22), 271 (M⁺, 100).

Anal. Calcd for C₁₅H₁₇N₃O₂·0.2 H₂O: C, 65.53; H, 6.37; N, 15.28. Found: C, 65.80; H, 6.22; N, 15.13.

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Example 76

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole)acetamide.* Making use
of the experimental procedure described in the above experiment, 2-acetamido-N-
benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), BBr_3 (1 M CH_2Cl_2 solution, 8.8 mL,
5 8.8 mmol), Et_3N (1.62 g, 1.60 mmol), and imidazole (0.60 g, 8.8 mmol) gave 0.60 g
(30%) of the desired product. It was recrystallized from ethyl acetate/hexane as a
10 beige colored solid: mp 146-148 °C; R_f 0. (7% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ
1.85 (s, COCH₃), 4.30 (br s, CH₂), 6.53 (d, J = 8.0 Hz, CH), 6.89 (s, C₅H), 7.12-7.33
15 (m, C₄H, 5PhH), 7.69 (s, C₂H), 9.06 (br s, NH), 9.29 (d, J = 8.0 Hz, NH); ¹³C NMR
(DMSO-d₆) 22.28 (COCH₃), 42.36 (CH₂), 61.18 (CH), 117.56 (C₅), 126.92 (C₄), 127.16
(2C₂ or 2C₃'), 128.19 (C₄), 128.26 (2C₂' or 2C₃'), 136.21 (C₂), 138.27 (C₁'), 165.72
(CONH), 169.77 (COCH₃) ppm; mass spectrum, FD (relative intensity) 274 (M⁺⁺2,
12), 273 (M⁺⁺1, 77), 272 (100), 205 (34), 274 (18).

Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;
H, 6.09; N, 20.32.

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Example 77

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole)acetamide.* A solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.60 g, 14.4 mmol) and BBr_3 (1 M CH_2Cl_2 solution, 15.8 mL, 15.8 mmol)) was prepared in THF (250 mL) and cooled to -78 °C. A solution of triethylamine (2.91 g, 28.8 mmol) in THF (20 mL) was then added to the above solution. This was followed by the addition of THF (30 mL) solution of pyrazole (1.17 g, 17.28 mmol) and the mixture thus obtained was stirred at -78 °C (30 min) and room temperature (1 h). The insoluble materials were filtered and the solvents removed from the filtrate *in vacuo*. The residue was then purified by flash column chromatography on silica gel using 4% MeOH/CHCl₃ as the eluant to give 0.80 g (22%) of the desired product. It was then recrystallized from EtOAc as a white solid: mp 158-160 °C; R_f 0.51 (6% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.93 (s, COCH₃), 4.29 (d, J = 5.8 Hz, NH), 6.26 (s, C₄H), 6.57 (d, J = 8.8 Hz, CH), 7.15-7.33 (m, 5PhH), 7.48 (br s, C₅H), 7.76 (br s, C₃H), 8.96 (t, J = 5.8 Hz, NH), 9.23 (d, J = 8.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.41 (COCH₃), 42.40 (CH₂), 65.51 (CH), 105.37 (C₄), 126.87 (C_{4'}), 127.14 (2C_{2'} or 2C_{3'}), 128.25 (2C_{2'} or 2C_{3'}), 129.00 (C₅), 138.59 (C₃), 139.17 (C_{1'}), 165.68 (CONH), 169.81 (COCH₃) ppm; mass spectrum, m/e (relative intensity) 273 (M⁺+1, 11), 272 (M⁺, 2), 139 (83), 138 (100), 92 (37).

25 Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 5.96; N, 20.28.

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Example 78

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole))acetamide.* Using 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), BBr_3 (1 M CH_2Cl_2 solution, 17.6 mL, 17.6 mmol), Et_3N (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g, 5 20.8 mmol), 1.20 g (28%) of the desired product was obtained. It was recrystallized from EtOAc as an amorphous white solid: mp 146-148 °C; R_f 0.48 (6% MeOH/ CHCl_3); ^1H NMR (DMSO-d_6) δ 1.85 (s, COCH_3), 4.32 (br s, CH_2), 6.70 (d, J = 7.8 Hz, CH), 7.21-7.29 (m, 5PhH), 8.01 (s, C_3H), 8.57 (s, C_5H), 9.04 (br s, NH), 9.39 (d, J = 7.8 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.39 (COCH_3), 42.59 (CH_2), 65.02 (CH), 126.97 (C_4'), 127.25 (2 C_2' or 2 C_3'), 128.32 (2 C_2' or 2 C_3'), 138.47 (C_1'), 143.93 (C_5), 151.50 (C_3), 164.77 (CONH), 170.23 (COCH_3) ppm; mass spectrum, FD (relative intensity) 275 (M $^{+}+2$, 12), 274 (M $^{+}+1$, 100), 273 (11), 205 (19), 204 (13), 140 (67), 139 (31).
15 Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_5\text{O}_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37; H, 5.66; N, 25.38.

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Example 79

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole))acetamide.* Making use of
2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr_3 (1 M CH_2Cl_2
solution, 13.2 mL, 13.2 mmol), Et_3N (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6
5 mmol), 0.90 g (27%) of the desired product was obtained as a white solid. It was
recrystallized from EtOH: mp 169-171 °C; R_f 0.22 (4% MeOH/CHCl₃); ¹H NMR
(DMSO-d₆) δ 1.97 (s, COCH₃), 4.25-4.40 (m, CH₂), 7.05 (d, J = 8.4 Hz, CII), 7.21-7.38
(m, 5PhH), 9.23 (t, J = 5.5 Hz, NH), 9.44 (s, C₅H), 9.69 (d, J = 8.4 Hz, NH); ¹³C NMR
10 (DMSO-d₆) 22.38 (COCH₃), 42.78 (CH₂), 63.62 (CH), 127.10 (C_{4'}), 127.39 (2C_{2'} or
2C_{3'}), 128.38 (2C_{2'} or 2C_{3'}), 138.26 (C_{1'}), 143.67 (C₅), 163.88 (CONH), 170.62 (COCH₃)
ppm; mass spectrum, FD (relative intensity) 275 (M⁺ 79), 273 (14), 206 (100), 205
(50).

15 Anal. Calcd for C₁₂H₁₄N₆O₂: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75;
H, 5.33; N, 30.64.

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Example 80

1 Preparation of α -acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

5 Preparation of 2-acetamido-2-bromo-N-benzylacetamide.

A solution of 2-acetamido-2-ethoxy-N-benzylacetamide (2.00 g, 8 mmol) in dry CH₂Cl₂ (200 mL) was stirred at room temperature as a solution of BBr₃ (8.8 mL, 8.8 mmol, 1.0 M in CH₂Cl₂) was introduced by means of a syringe under a nitrogen atmosphere. A white mist formed and after it disappeared, the N₂ line was removed and the reaction sealed. The resulting yellow solution was stirred (3.5 h) and then concentrated in vacuo to give yellow crystals of 2-acetamido-2-bromo-N-benzyl acetamido which was stored under vacuum overnight.

Preparation of 2-pyridyllithium.

The generation of 2-pyridyllithium in situ was run under nitrogen. A solution of n-butyllithium (7.2 mL, 2.5 M solution in hexane, 18 mmol) was added to dry ether (60 mL), cooled to -20 °C, and stirred as 2-bromopyridine (1.6 mL, 17 mmol) in dry ether (15 mL) was added dropwise (15 min). The resulting blood red solution was stirred at -20 °C for an additional 5 minutes and then transferred through a doubled-ended needle under a stream of nitrogen to an addition funnel where it was cooled to -78 °C.

30 Preparation of α -acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The cooled 2-pyridyllithium solution was added dropwise (approximately 2 drops per second) to the solution of 2-acetamido-2-bromo-N-benzylacetamide in dry THF (200 mL) and maintained at -78 °C. The reaction mixture was stirred for an additional 30-45 minutes at -78 °C. The reaction was quenched with saturated aqueous solution of NH₄Cl (40 mL) at -78 °C producing a heterogenous mixture

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1 Na_2CO_3 was added dropwise until the precipitate dissolved. The organic layer
was separated and then the aqueous layer was extracted with ether ($2 \times 50 \text{ mL}$).
The combined organic layers were dried (Na_2SO_4), concentrated under vacuum
5 and separated using flash chromatography on silica gel with ethyl acetate as the
eluent. The fractions containing the products were concentrated under vacuum,
separated and then further purified by column chromatography on alumina
10 (80-200 mesh, Grade 1, Fisher) employing ethyl acetate as the solvent. Fractions
containing α -acetamido-N-benzyl-2-pyridylacetamide were concentrated to dryness
and gave a white amorphous solid (250 mg, 11% yield); $R_f = 0.39$ (5%
 $\text{CH}_3\text{OH}/\text{CHCl}_3$); mp 146-147 °C; IR (KBr) 3290, 3180, 3020, 1620 br, 1580, 1520 br,
1480, 1420, 1370, 1310, 1260 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d₆) δ 1.96 (s, 3H), 4.28
15 (d, $J = 5.8 \text{ Hz}$, 2H), 5.59 (d, $J = 8.0 \text{ Hz}$, 1H), 7.18 - 7.30 (m, 5H), 7.32 (dd, $J = 7.7, 5.2 \text{ Hz}$, 1H), 7.47 (d, $J = 7.7 \text{ Hz}$, 1H), 7.80 (dt, $J = 7.7, 1.5 \text{ Hz}$, 1H), 8.55 (m, 2H), 8.78 (br t, $J = 5.8 \text{ Hz}$, 1H); ^{13}C NMR (75 MHz, DMSO-d₆) 22.5, 42.1, 58.3, 121.7, 122.8, 126.6,
20 126.9 (2C), 128.1 (2C), 136.8, 139.1, 148.6, 157.2, 169.0, 169.2 ppm; FD (Lilly) mass spectrum, m/e (relative intensity) 284 ($M^{++} + 1$, 6), 283 (M^+ , 0.8), 151 (8), 150 (100), 141 (4). $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2$

Anal. Calcd for C 67.83, H, 6.05, N, 14.83

Found: C, 68.11, H, 6.00, N, 14.89.

25 Fractions containing 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide were
combined, concentrated in vacuo and yielded a white amorphous solid: (150 mg,
6% yield). R_f 0.34 (5% $\text{CH}_3\text{OH}/\text{CHCl}_3$); mp 226 decomposed (recrystallized in
ethanol) ^1H NMR (300 MHz, DMSO-d₆) δ 1.94 s, 4.26 (dd, $J = 15.2, 5.7 \text{ Hz}$, 1H), 4.33
30 (dd, $J = 15.2, 6.1 \text{ Hz}$, 1H), 6.26 (br t, $J = 6.8 \text{ Hz}$, 1H), 6.37 (br d, $J = 9.1 \text{ Hz}$, 1H), 6.69 (d,
 $J = 8.7 \text{ Hz}$, 1H), 7.22-7.33 (m, 5H), 7.42 (ddd, $J = 9.1, 6.8, 1.6 \text{ Hz}$, 1H), 7.58 (dd, $J = 6.8,$
 1.6 Hz , 1H), 8.93 (br t, $J = 5.8 \text{ Hz}$, 1H), 9.20 (d, $J = 8.7 \text{ Hz}$, 1H); ^{13}C NMR (75 MHz,
35 DMSO-d₆) 22.5, 42.5, 62.5, 105.1, 119.4, 126.80, 127.10 (2C), 128.2 (2C), 135.6, 138.8,
140.2, 161.2, 166.0, 170.0 ppm. Hydrogen and carbon assignments were verified
with $^1\text{H}-^1\text{H}$ COSY, $^1\text{H}-^{13}\text{C}$ -COSY, zero quantum NMR experiments. The
structure was confirmed by X-ray crystallography.

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1 Preparation of authentic 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The generation of 2-hydroxypyridylsodium *in situ* was done under anhydrous conditions. A solution of 2-hydroxypyridine (1.57 g, 16 mmol, vacuum dried, 97% Aldrich) in dry THF (200 mL) was stirred and cooled to 0°C and then NaH (0.77 g, 60% in mineral oil, 19.2 mmol) was added in one portion leading to the evolution of H₂ and the generation of a heterogeneous mixture. A solution of 2-acetamido-2-bromo-N-benzylacetamide (8 mmol based on 2-acetamido-2-ethoxy-N-benzylacetamide) in dry THF (160 mL) was then transferred through a double-ended needle by means of a stream of nitrogen. The resulting mixture was quenched with saturated aqueous solution of NH₄Cl (50 mL) at 0°C producing a white precipitate. A saturated aqueous solution Na₂CO₃ was added dropwise while stirring at 0°C until all of the white precipitate dissolved. The two layers were separated while cold and then the aqueous fraction was extracted with THF (2 x 100 mL). The combined organic layers were dried (Na₂SO₄), and concentrated to dryness. The crude reaction mixture residue was dissolved in a minimum of CHCl₃ and was flash chromatographed on a silica gel column using ethyl acetate as the eluent and gave a white amorphous solid (1.10 g, 46% yield) which was identical to properties previously observed for 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide: R_f 0.34 (5% CH₃OH/CHCl₃); mp 162-163.5 °C (recrystallized in ethyl acetate); IR (KBr) 3300, 3280, 3260, 3080, 1690, 1680, 1650 br, 1580, 1570, 1520, 1490, 1140 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.96 (s, 3H), 4.27 (dd, J = 15.3, 5.8 Hz, 1H), 4.36 (dd, J = 15.3, 6.2 Hz, 1H), 6.27 (dt, J = 6.8, 1.1 Hz, 1H), 6.39 (bd, J = 8.9 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 7.22-7.34 (m, 5H), 7.43 (ddd, J = 8.9, 6.8, 1.9 Hz, 1H), 7.59 (dd, J = 6.8, 1.9 Hz, 1H), 8.93 (br t, J = 5.9 Hz, 1H), 9.20 (d, J = 8.7 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆) 22.4, 42.5, 62.5, 105.1, 119.4, 126.8, 127.1 (2C), 128.2 (2C), 135.6, 138.8, 140.1, 161.1, 166.0, 169.9 ppm; FD (Lilly) mass spectrum, m/e (relative intensity) 598 (2M, 2), 300 (M⁺⁺¹, 17), 299 (M⁺, 100), 96 (2), 95 (26). C₁₆H₁₇N₃O₃.

Anal. Calcd for C, 64.20, H 5.73, N 14.04.

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EXAMPLE 81 α -acetamido-N-benzyl-2-pyridyl acetamide N-oxide

To a cooled solution of 2- α -acetamido-N-benzyl-2-pyridylacetamide dissolved in dry THF is added m-perchloroperbenzoic acid to give the resulting product.

Similarly, using the procedure described hereinabove, the following examples are prepared.

2-acetamido-N-benzyl-2-(3-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-pyrimidinyl)acetamide and the N-oxide thereof

2-acetamido-N-benzyl-2-(4-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(5-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(3-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyrazinyl) acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-thiazolyl)acetamide,

2-acetamido-N-benzyl-2-(2-oxazolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isoxazolyl)acetamide,

2-acetamido-N-benzyl-2-(5-isoxatolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isothiazolyl)acetamide, and

2-acetamido-N-benzyl-2-(5-isothiazolyl)acetamide.

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General Procedure. 2-Acetamido-N-benzyl-2-ethoxyacetamide (1equiv.) was suspended in anhydrous ethyl ether, and then boron trifluoride etherate (1.6-6.3 equiv.) was rapidly added and the resulting solution was stirred for 15 min. The aromatic substrate (1.6-16 equiv.) was then added and the reaction was stirred at room temperature (1-7 days).

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EXAMPLE 82

1 α -Acetamido-N-benzyl-2-(S-thiophenoxy)-acetamide
(II). The reaction mixture was treated with an aqueous
saturated NaHCO_3 solution and the white insoluble solid was
filtered and then washed successively with H_2O and hexanes.
5 The desired product was purified by recrystallization from
chloroform hexanes to give II in 94% yield: R_f 0.43 (97:3
chloroform/methanol); m.p. 165-167°: i.r. (KBr) 3280, 1630
(br), 1520 (br), 1430, 1365, 1280, 1245, 1180 cm^{-1} ; ^1H n.m.r.
10 (DMSO-d₆) 81.83 (s, CH_3CO). 4.22-4.36 (m. CH_2), 5.90 (d, J =
9.0 Hz, NH), 8.84 (t, J = 5.4 Hz, NH); ^{13}C n.m.r. (DMSO-d₆)
22.34 (CH_3CO), 42.25 (CH_2), 57.65 (CH), 126.86 (C_4'), 127.20
($2\text{C}_2'$), 123.73 (C_4'), 128.28 ($2\text{C}_2'$ or $2\text{C}_3'$), 128.88 ($2\text{C}_2'$ or $2\text{C}_3'$),
132.36 ($2\text{C}_3'$), 132.51 (C_1'), 138.76 (C_1'), 167.09 (CONH), 168.97
(CH_3CO) ppm; mass spectrum, m/e (relative intensity) 315 (M +
1,1), 205 (17), 163 (40), 138 (8), 110 (90), 109 (29), 106
15 (96), 93 (35), 91 (100).

20 Anal. calc. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C 64.94, H 5.77. Found: C 65.27, H
5.54.

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Example 83

1 *Synthesis of α-Acetamido-N-benzyl-2-(tetrahydrofuran)acetamide (3).* A
methanolic solution (70 mL) of α-acetamido-N-benzyl-2-furanacetamide (3.50 g,
12.85 mmol) was hydrogenated (35-40 psi) in the presence of Pd/C (10%, 0.44 g) (44
5 h). The catalyst was filtered through celite, washed with MeOH (10 mL) and the
filtrate concentrated to dryness *in vacuo* to give 3a and 3b (3.50 g) as a white solid.
The products were fractionally recrystallized from EtOAc to give 1.30 g (37%) of 3a:
mp 159-161 °C; R_f 0.38 (6% MeOH/CHCl₃); IR (KBr) 3340 (br), 3000, 1600, 1550 (br),
10 1420, 1350, 720, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.66-1.90 (m, C₃H₂, C₄H₂), 1.85
(C(O)CH₃), 3.62-3.68 (m, C₅HH'), 3.75-3.80 (m, C₅HH'), 3.98-4.00 (m, C₂H), 4.26-4.38
(m, CH, CH₂), 7.18-7.32 (m, 5 PhH), 8.11 (d, J = 8.8 Hz, NH), 8.52 (t, J = 5.8 Hz,
NH); ¹³C NMR (DMSO-d₆) 22.52 (C(O)CH₃), 24.78 (C₃), 27.82 (C₄), 41.96 (CH₂), 55.67
15 (CH), 67.54 (C₅), 78.48 (C₂), 126.58 (C₄'), 127.97 (2C₂' or 2C₃'), 128.12 (2C₂' or 2C₃'),
139.27 (C₁'), 169.09 (C(O)NH), 170.09 (C(O)CH₃) ppm; mass spectrum m/e (relative
intensity) 277 (M⁺⁺1, 4), 206 (52), 142 (13), 106 (38), 91 (100), 71 (97). Anal.
(C₁₅H₂₀N₂O₃) C, H, N.

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1 The remaining EtOAc mother liquor after recrystallization was
concentrated to half its volume and hexane was added dropwise while heating
until the solution became turbid. A white solid (0.65 g, 18%) separated on cooling
5 and was collected by filtration to give diastereoisomer 3b: mp 130-132 °C; R_f 0.38
(6% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.55-1.86 (m, C₃H₂, C₄H₂), 1.89 (s,
C(O)CH₃), 3.55-3.64 (m, C₅HH'), 3.70-3.78 (m, C₅HH'), 4.08-4.11 (m, C₂H), 4.27 (d, J
= 5.8 Hz, CH₂), 4.36 (dd, J = 4.7, 8.6 Hz, CH), 7.21-7.32 (m, 5 PhH), 7.94 (d, J = 8.6
10 Hz, NH), 8.39 (t, J = 5.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.45 (C(O)CH₃), 25.16 (C₄),
27.53 (C₃), 42.04 (CH₂), 55.48 (CH), 67.53 (C₅), 78.26 (C₂), 126.59 (C₄'), 127.04 (2C₂' or
2C₃'), 128.10 (2C₂' or 2C₃'), 139.21 (C₁'), 169.55 (C(O)NH), 169.79 (C(O)CH₃) ppm;
mass spectrum m/e (relative intensity) 277 (M⁺+1, 4), 206 (50), 142 (23), 106 (39), 91
15 (100), 71 (96). Anal. (C₁₅H₂₀N₂O₃) C, H, N.

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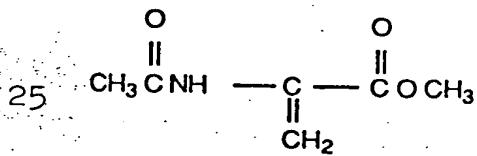
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Example 84

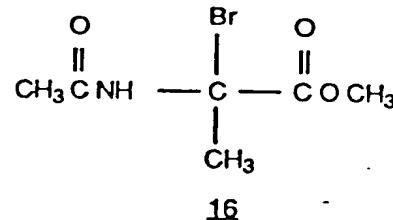
1 *Synthesis of Methyl α-Acetamido-2-methyl-2-furanacetate (17).* HBr was bubbled (2.5 min) through a CDCl_3 solution (25 mL) of 15 (3.80 g, 26.6 mmol). The excess HBr and CDCl_3 were removed by evaporating the solution with a
5 continuous stream of Ar (20-30 min). The light yellow oily residue that remained containing 16 was dissolved in THF (100 mL), and then furan (32.76 g, 482.0 mmol) and ZnCl_2 (1 M in ether, 53.0 mL, 53.0 mmol) were added. The reaction was stirred at room temperature (3.5 h) and then treated with H_2O (50 mL). The
10 aqueous mixture was extracted with EtOAc (3×100 mL), and the combined extracts were dried (Na_2SO_4). The volatile materials were removed by distillation *in vacuo* to give 5.00 g (89%) of 17: R_f 0.35 (50%, EtOAc/ CHCl_3); ^1H NMR (CDCl_3) δ 1.94 (s, CH_3), 1.99 (s, $\text{C}(\text{O})\text{CH}_3$), 3.74 (s, $\text{C}(\text{O})\text{OCH}_3$), 6.36 (br s, C_3H , C_4H), 6.83 (s, NH), 7.35 (s, C_5H); ^{13}C NMR (CDCl_3) 21.43 (CH_3), 23.26 ($\text{C}(\text{O})\text{CH}_3$), 53.03 ($\text{C}(\text{O})\text{OCH}_3$), 58.36 ($\text{C}(\text{CH}_3)$), 107.39 (C_4), 110.52 (C_3), 142.10 (C_5), 152.03 (C_2), 169.21 ($\text{C}(\text{O})\text{CH}_3$), 171.34 ($\text{C}(\text{O})\text{OCH}_3$) ppm.

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Example 85

1 *Synthesis of α -Acetamido-2-methyl-2-furanacetic Acid (18).* A 95% EtOH
solution (150 mL) of 17 (5.00 g, 23.6 mmol) and KOH (3.00 g, 53.5 mmol) was stirred
at room temperature (48 h). The solvent was removed and the residue was
5 dissolved in H₂O (50 mL). The aqueous solution was washed with Et₂O (3 × 50 mL)
and then acidified to pH 1.5 with 10% H₃PO₄. The acidified solution was extracted
with EtOAc (3 × 200 mL) and the combined extracts were dried (Na₂SO₄), and
concentrated *in vacuo* to give 2.90 g (62%) of 18: mp 178-180 °C (d) (recrystallized
10 from CH₃CN); IR (KBr) 3400 (br), 1700 (br) cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.67 (s,
CH₃), 1.83 (s, C(O)CH₃), 6.39 (m, C₃H, C₄H), 7.59 (s, C₅H), 8.34 (s, NH), 12.63 (s,
C(O)OH); ¹³C NMR (DMSO-d₆) 22.20 (C(O)CH₃), 22.59 (CH₃), 57.65 (C(CH₃)), 107.09
15 (C₄), 110.49 (C₃), 142.33 (C₅), 153.36 (C₂), 168.86 (C(O)NH), 171.78 (C(O)OH) ppm;
mass spectrum, m/e (relative intensity) 198 (M⁺⁺, 4), 143 (97), 152 (63), 140 (23),
111 (73), 110 (100), 94 (24). Anal. (C₉H₁₁NO₄).C, H, N.

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Example 86

Synthesis of α -Acetamido-N-benzyl-2-methyl-2-furanacetamide (4).

1 Employing the mixed carbonic anhydride coupling procedure^{5,9} with 18 (2.40 g, 12.2 mmol), 4-methylmorpholine (1.23 g, 12.2 mmol), isobutylchloroformate (1.83 g, 13.4 mmol), and benzylamine (1.43 g, 12.7 mmol) gave 4 (1.50 g, 43%) as a thick oil: R_f 0.29 (2% MeOH/CHCl₃); ¹H NMR (CDCl₃) δ 1.94 (s, CH₃), 1.98 (s, C(O)CH₃), 4.40 (d, J = 5.6 Hz, CH₂), 6.20 (br s, NH), 6.34-6.37 (m, C₃H, C₄H), 7.05-7.36 (m, NH, C₅H, 5 PhH); ¹³C NMR (CDCl₃) 22.31 (C(O)CH₃), 23.81 (CH₃), 43.77 (CH₂), 58.50 (C(CH₃)), 107.94 (C₄), 110.67 (C₃), 126.99 (2C_{2'} or 2C_{3'}), 127.41 (C_{4'}), 128.60 (2C_{2'} or 2C_{3'}), 137.52 (C_{1'}), 142.38 (C₅), 152.94 (C₂), 169.03 (C(O)NH), 171.16 (COCH₃) ppm; mass spectrum, m/e (relative intensity) 287 (M⁺+1, 4), 228 (4), 153 (99), 152 (96), 138 (15), 111 (63), 110 (100), 91 (75); M_r (EI) 286.13074 (calcd for C₁₆H₁₈N₂O₃, 286.13174).

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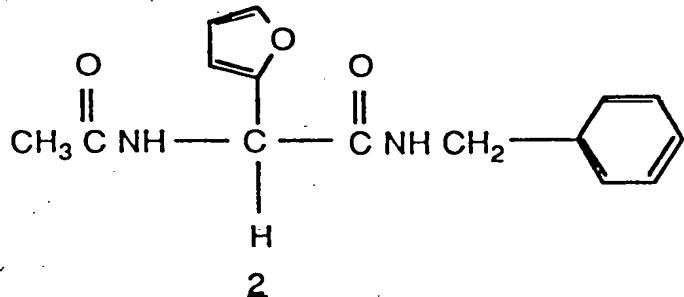
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Example 87

1 *Synthesis of α -Thioacetamido-N-benzyl-2-furanacetamide (5).* A THF
solution (80 mL) of **2** (1.00 g, 3.68 mmol) and Lawesson's reagent (0.73 g, 1.84
mmol) was stirred at room temperature (4 h). The THF was removed *in vacuo*
5 and the residue was purified by flash column chromatography on SiO₂ gel using
1% MeOH/CHCl₃ to give 0.75 g (71%) of **5**: mp 78-80 °C; R_f 0.51 (1% MeOH/CHCl₃);
IR (KBr) 3200 (br), 1630, 1500, 1440, 1350, 790, 710, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ
10 2.46 (s, C(S)CH₃), 4.27-4.35 (m, CH₂), 6.22 (d, J = 7.7 Hz, CH), 6.32 (d, J = 3.3 Hz,
C₃H), 6.41-6.44 (m, C₄H), 7.15-7.33 (m, 5 PhH), 7.64 (s, C₅H), 8.81 (t, J = 5.9 Hz,
NH), 10.54 (d, J = 7.7 Hz, NH); ¹³C NMR (DMSO-d₆) 32.70 (s, C(S)CH₃), 42.39 (CH₂),
56.82 (CH), 108.76 (C₃), 110.67 (C₄), 126.81 (C_{4'}), 127.12 (2C_{2'} or 2C_{3'}), 128.23 (2C_{2'} or
2C_{3'}), 139.98 (C_{1'}), 143.06 (C₅), 149.53 (C₂), 166.55 (C(O)NH), 200.68 (C(S)CH₃) ppm;
15 mass spectrum (FD) 288 (M⁺). Anal. (C₁₅H₁₆N₂O₂S) C, H, N.



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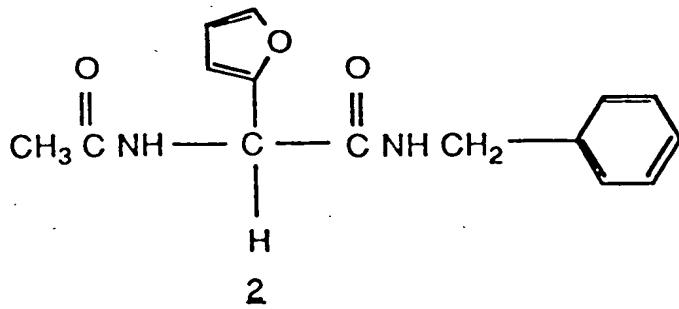
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Example 88

1 *Synthesis of α -Thioacetamido-N-benzyl-2-furanthioacetamide (6).* A THF
solution (90 mL) of 2 (2.00 g, 7.35 mmol) and Lawesson's reagent (3.27 g, 8.09
mmol) was heated to reflux (4 h). The THF was removed *in vacuo* and the residue
5 was purified by two successive flash column chromatographies on SiO₂ gel using
0.5% MeOH/CHCl₃ as the eluant in the first chromatography and CHCl₃ in the
second chromatography. Compound 6 (0.50 g, 22%) was then further purified by
preparative TLC (CHCl₃): mp 99-101 °C; R_f 0.74 (1% MeOH/CHCl₃); IR (KBr) 3100,
10 1580, 1500 (br) cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.58 (s, C(S)CH₃), 4.86 (dd, J = 5.4, 15.0
Hz, CHH), 4.96 (dd, J = 5.4, 15.0 Hz, CHH), 6.49-6.55 (m, C₃H, C₄H), 6.65 (d, J = 7.5
Hz, CH), 7.31-7.43 (m, 5 PhH), 7.75 (s, C₅H) 10.64 (d, J = 7.5 Hz, NH), 10.95 (t, J =
5.4 Hz, NH); ¹³C NMR (DMSO-d₆) 32.79 (s, C(S)CH₃), 48.30 (CH₂), 61.88 (CH),
15 108.50 (C₃), 110.53 (C₄), 127.05 (C_{4'}), 127.48 (2C_{2'} or 2C_{3'}), 128.19 (2C_{2'} or 2C_{3'}),
136.67 (C_{1'}), 142.91 (C₅), 150.15 (C₂), 197.45 (C(S)NH), 200.56 (C(S)CH₃) ppm; mass
spectrum (FD) 304 (M⁺). Anal. (C₁₅H₁₆N₂OS₂) C, H, N,

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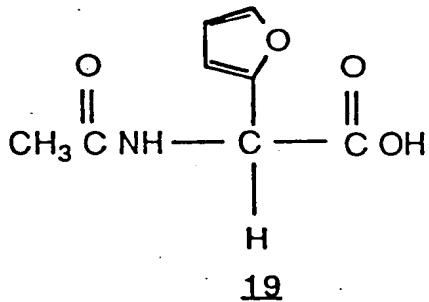
Example 89

1 *Synthesis of α-Acetamido-N-(3-pyridinylmethyl)-2-furanacetamide (7).*

Using racemic **19** (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39 mmol), isobutylchloroformate (2.24 g, 16.39 mmol), and 3-aminomethylpyridine (1.77 g, 5 16.39 mmol) in the mixed carbonic anhydride protocol gave 3.35 g (75%) of **7**: mp 172-174 °C (recrystallized from EtOAc); R_f 0.27 (8% MeOH/CHCl₃); IR (KBr) 3400, 3300, 1640, 1540, 1420, 1360, 820, 740 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.32 (d, *J* = 5.8 Hz, CH₂), 5.55 (d, *J* = 7.9 Hz, CH), 6.28-6.29 (m, C₃H), 6.41-6.43 (m, 10 C₄H), 7.32 (dd, *J* = 4.8, 7.7 Hz, C_{5'}H), 7.58-7.62 (m, C_{4'}H, C₅H), 8.44 (br s, C_{2'}H, C₆'H), 8.62 (d, *J* = 7.9 Hz, NH), 8.81 (t, *J* = 5.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.31 (C(O)CH₃), 39.98 (CH₂), 50.94 (CH), 107.67 (C₄), 110.54 (C₃), 123.38 (C_{5'}), 134.57 (C_{3'}), 134.83 (C_{4'}), 142.64 (C₅), 148.06 (C_{6'}), 148.55 (C_{2'}), 150.94 (C₂), 168.19 (C(O)NH), 169.26 (C(O)CH₃) ppm; mass spectrum (FD) 274 (M⁺⁺¹). Anal. (C₁₄H₁₅N₃O₃) C, H, N.

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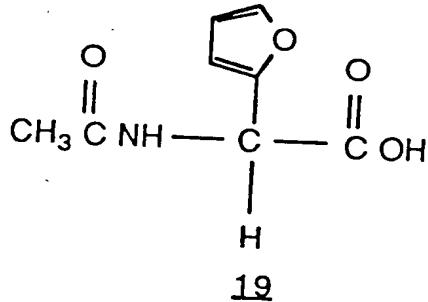
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Example 90

1 *Synthesis of α -Acetamido-N-(4-pyridinylmethyl)-2-furanacetamide (8).*
Making use of racemic 19 (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39
mmol), isobutylchloroformate (2.24 g, 16.39 mmol), and 4-aminomethylpyridine
5 (1.77 g, 16.39 mmol) in the mixed carbonic anhydride method, gave 3.40 g (76%)
of 8: mp 168-170 °C (recrystallized from EtOAc); R_f 0.31 (8% MeOH/CHCl₃); IR
(KBr) 3180, 1650 (br), 1480, 1400, 1340, 780, 740 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.90 (s,
C(O)CH₃), 4.32 (d, J = 5.7 Hz, CH₂), 5.57 (d, J = 7.8 Hz, CH), 6.32-6.34 (m, C₃H),
10 6.42-6.43 (m, C₄H), 7.19 (d, J = 4.9 Hz, C_{3'}H, C_{5'}H), 7.64 (s, C₅H), 8.46 (d, J = 4.9 Hz,
C_{2'}H, C_{6'}H), 8.64 (d, J = 7.8 Hz, NH), 8.84 (t, J = 5.7 Hz, NH); ¹³C NMR (DMSO-d₆)
22.27 (C(O)CH₃), 41.26 (CH₂), 50.99 (CH), 107.74 (C₄), 110.54 (C₃), 121.87 (C_{3'}, C_{5'}),
15 142.63 (C₅), 148.17 (C_{4'}), 149.35 (C_{2'}, C_{6'}), 150.82 (C₂), 168.35 (C(O)NH), 169.29
(C(O)CH₃) ppm; mass spectrum (FD) 274 (M⁺⁺¹). Anal. (C₁₄H₁₅N₃O₃) C, H, N.

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Example 91

Synthesis of α -Acetamido-N-(1-oxo-3-pyridinylmethyl)-2-furanacetamide

(9). A solution of 1 (1.50 g, 5.49 mmol) and m-chloroperoxybenzoic acid (1.90 g, 6.04 mmol) in THF (175 mL) was heated to reflux (3 h) and then cooled to room temperature. The THF solution was concentrated to approximately half its volume, and then cooled to give 1.00 g (63%) of 2: mp 159-161 °C (recrystallized from EtOH); R_f 0.30 (20% MeOH/CHCl₃); IR (KBr) 3400 (br), 1620, 1500 (br), 1420, 1350, 750 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.27 (d, J = 5.0 Hz, CH₂), 5.53 (d, J = 7.6 Hz, CH), 6.31 (br s, C₃H), 6.42 (br s, C₄H), 7.14-7.18 (m, 1 ArH), 7.31-7.37 (m, 1 ArH), 7.61 (br s, C₅H), 8.07 (s, 2 ArH), 8.63 (br s, NH), 8.80 (br s, NH); ¹³C NMR (DMSO-d₆) 22.29 (C(O)CH₃), 39.36 (CH₂), 50.99 (CH), 107.79 (C₄), 110.56 (C₃), 124.03 (C_{4'}), 126.10 (C_{5'}), 137.16 (C_{3'}), 137.31 (C_{6'}), 138.70 (C_{2'}), 142.69 (C₅), 150.72 (C₂), 168.40 (C(O)NH), 169.32 (C(O)CH₃) ppm; mass spectrum (FD) 289 (M⁺); M_r (EI) 289.10554 (calcd for C₁₄H₁₅N₃O₄, 289.10626).

Anal. Calcd for C₁₄H₁₅N₃O₄·2.0 H₂O: C, 51.69; H, 5.89; N, 12.92. Found: C, 52.03; H, 5.56; N, 13.36.

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Example 92

1 *Synthesis of α-Acetamido-N-(1-oxo-4-pyridinylmethyl)-2-furanacetamide (10).* Following the preceding procedure and using δ (1.50 g, 5.49 mmol) and m-chloroperoxybenzoic acid (1.90 g, 6.04 mmol) gave a light yellow solid (0.96 g, 60%)
5 directly upon cooling the THF solution. The precipitate was filtered and recrystallized from EtOH to give 10: mp 210-212 °C (d); R_f 0.25 (20% MeOH/CHCl₃); IR (KBr) 3300, 1620, 1500, 1410, 1350, 740 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.26 (d, J = 5.8 Hz, CH₂), 5.52 (d, J = 7.7 Hz, CH), 6.30 (br s, C₃H), 6.41-10 6.42 (m, C₄H), 7.21 (d, J = 6.8 Hz, C_{3'}H, C_{5'}H), 7.63 (s, C₅H), 8.14 (d, J = 6.8 Hz, C_{2'}H, C_{6'}H), 8.62 (d, J = 7.7 Hz, NH), 8.82 (t, J = 5.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.35 (C(O)CH₃), 40.68 (CH₂), 51.14 (CH), 107.87 (C₄), 110.62 (C₃), 124.83 (C_{3'}, C_{5'}), 137.43 (C_{4'}), 138.39 (C_{2'}, C_{6'}), 142.72 (C₅), 150.77 (C₂), 168.48 (C(O)NH), 169.45 (C(O)CH₃) ppm; mass spectrum (FD) 289 (M⁺). Anal. (C₁₄H₁₅N₃O₄) C, H, N.

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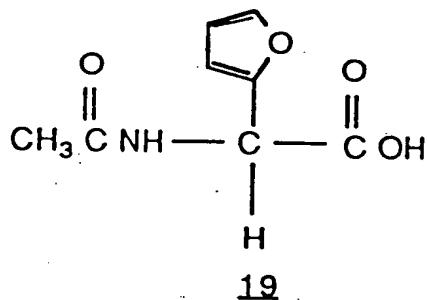
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Example 93

1 *Synthesis of α -Acetamido-2-furanacetic-2'-pyridinehydrazide (11).*

Following the mixed carbonic anhydride procedure and using racemic 19 (2.00 g, 10.39 mmol), 4-methylmorpholine (1.10 g, 10.93 mmol), isobutylchloroformate 5 (1.49 g, 10.93 mmol), and 2-hydrazinopyridine (1.20 g, 11.00 mmol) gave an insoluble material upon workup containing 11 and 4-methylmorpholine hydrochloride. The reaction products were suspended in EtOH (25 mL), and 11 10 (1.00 g) was collected by filtration. Concentration of the THF filtrate and trituration of the residue with EtOAc gave an additional 0.70 g of 11 to give a combined yield of 1.70 g (64%): mp 226-228 °C (recrystallized from EtOH); R_f 0.30 (10% MeOH/CHCl₃); IR (KBr) 3400, 1650, 1580, 1440, 1360, 1320, 770, 730 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.83 (s, C(O)CH₃), 5.64 (d, J = 8.0 Hz, CH), 6.41-6.50 (m, C₃H, C₄H, C₅'H), 6.67 (dd, J = 5.4, 6.7 Hz, C₃'H), 7.44-7.52 (m, C₄'H), 7.66 (s, C₅H), 8.02 (d, J = 4.0 Hz, C₆'H), 8.40 (s, C(O)NHNH), 8.66 (d, J = 8.0 Hz, NH), 10.20 (s, C(O)NHNH); ¹³C NMR (DMSO-d₆) 22.26 (C(O)CH₃), 49.56 (CH), 105.93 (C₃'), 107.87 (C₃), 110.57 (C₄), 114.50 (C₅'), 137.48 (C₄'), 142.76 (C₅), 147.45 (C₆'), 150.60 (C₂), 159.59 (C₂'), 167.88 (C(O)NH), 169.28 (C(O)CH₃) ppm; mass spectrum (FD) 274 (M⁺); M_r (EI) 274.10649 (calcd for C₁₃H₁₄N₄O₃, 274.10659).

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Example 94

1 *Synthesis of R(-)- α -Acetamido-N-(4-fluorobenzyl)-2-furanacetamide ((R)-12).*

Using (R)-19 (0.94 g, 5.1 mmol), 4-methylmorpholine (0.52 g, 5.1 mmol), isobutylchloroformate (0.70 g, 5.1 mmol), and 4-fluorobenzylamine (0.65 g, 5.16 mmol) in the mixed carbonic anhydride method gave 1.00 g (68%) of (R)-12: mp 205-207 °C (recrystallized from EtOAc); R_f 0.30 (4% MeOH/CHCl₃); $[\alpha]^{26}_D = -77.42$ (c=1, MeOH); IR (KBr) 3400 (br), 1620, 1580, 1500 (br), 1350, 770, 720 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.27 (d, $J = 5.9$ Hz, CH₂), 5.54 (d, $J = 8.0$ Hz, CH), 6.27 (d, $J = 3.0$ Hz, C₃H), 6.41 (dd, $J = 1.9, 3.0$ Hz, C₄H), 7.08-7.15 (m, 2 ArH), 7.20-7.26 (m, 2 ArH), 7.61 (d, $J = 1.9$ Hz, C₅H), 8.58 (d, $J = 8.0$ Hz, NH), 8.74 (t, $J = 5.9$ Hz, NH) ppm; addition of R(-) mandelic acid to a CDCl₃ solution of (R)-12 gave only one signal for the acetamide methyl protons. Mass spectrum (FD) 290 (M⁺).
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Anal. (C₁₅H₁₅FN₂O₃) C, H, N.

20 *Synthesis of R(-)- α -Acetamido-N-(4-methylbenzyl)-2-furanacetamide ((R)-13).*

Employing the mixed carbonic anhydride procedure and making use of (R)-19 (1.50 g, 8.20 mmol), 4-methylmorpholine (0.83 g, 8.20 mmol), isobutylchloroformate (1.12 g, 8.20 mmol), and 4-methylbenzylamine (0.99 g, 8.20 mmol) gave 1.80 g (77%) of (R)-13: mp 210-212 °C (recrystallized from EtOAc); R_f 0.54 (4% MeOH/CHCl₃); $[\alpha]^{26}_D = -74.43$ (c=1, MeOH); IR (KBr) 3400 (br), 1610 (br), 1500 (br), 1350, 1320, 780, 720 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 2.25 (s, CH₃), 4.24 (d, $J = 5.5$ Hz, CH₂), 5.56 (d, $J = 8.1$ Hz, CH), 6.28 (br s, C₃H), 6.41 (br s, C₄H), 7.09 (br s, 4ArH), 7.61 (br s, C₅H), 8.58 (d, $J = 8.1$ Hz, NH), 8.72 (t, $J = 5.5$ Hz, NH); addition of (R)(-)mandelic acid to a CDCl₃ solution of (R)-13 gave only one signal for the acetamide methyl protons. ¹³C NMR (DMSO-d₆) 20.64 (CH₃), 22.32 (C(O)CH₃), 42.00 (CH₂), 50.88 (CH), 107.52 (C₄), 110.50 (C₃), 127.06 (2C_{2'} or 2C_{3'}), 128.77 (2C_{2'} or 2C_{3'}), 135.82 (C_{1'} or C_{4'}), 135.98 (C_{1'} or C_{4'}), 142.51 (C₅), 151.21 (C₂), 167.87 (C(O)NH), 169.17 (C(O)CH₃) ppm; mass spectrum (FD) 287 (M⁺⁺¹). Anal.
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(C₁₆H₁₈N₂O₃) C, H, N.

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Example 95

1 *Synthesis of R(-)-Acetamido-N-(4-trifluoromethylbenzyl)-2-furanacetamide ((R)-14).* Using (R)-19 (1.00 g, 5.46 mmol), 4-methylmorpholine (0.55 g, 5.46 mmol), isobutylchloroformate (0.75 g, 5.46 mmol), and 4-trifluoromethylbenzyl-
5 amine (0.96 g, 5.46 mmol) in the mixed carbonic anhydride protocol gave 1.15 g
5 (59%) of (R)-14: mp 193-195 °C (recrystallized from EtOAc/hexane); $[\alpha]^{26}_D = -69.27$
(c=1, MeOH); IR (KBr) 3220, 1610, 1520, 1400, 1350, 800, 720 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.37 (d, $J = 5.8$ Hz, CH₂), 5.56 (d, $J = 7.9$ Hz, CH), 6.30-6.31
10 (m, C₃H), 6.41-6.43 (m, C₄H), 7.40-7.43 (m, 2ArH), 7.63-7.68 (m, 2ArH, C₅H), 8.61
(d, $J = 7.9$ Hz, NH), 8.44 (t, $J = 5.8$ Hz, NII); addition of (R)(-)-mandelic acid to a
CDCl₃ solution of (R)-14 gave only one signal for the acetamide methyl protons.
Mass spectrum (FD) 340 (M⁺). Anal. (C₁₆H₁₅F₃N₂O₃) C, H, N.

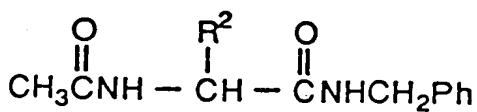
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GENERAL SYNTHESIS

General Synthesis - Several preparative routes were utilized for the construction of
the targeted compounds. In most cases, 2-acetamido-N-benzyl-2-aminoacetamide (2r) served as the starting material. Treatment of 2r with the appropriate
chloroformate, isocyanate, isothiocyanate, anhydride, or use of the mixed
anhydride protocol advanced for peptide synthesis led to the preparation of the N-
acyl substituted adducts 2e-2l and 2n. Correspondingly, the preformed α-bromo
derivative 2s was employed as the immediate precursor for 2m and 2p, while 2-
acetamido-N-benzyl-2-(trimethylammonio)acetamide tetrafluoroborate (2t) was
utilized for the synthesis of 2q. Finally, alkaline hydrolysis of 2p, followed by
neutralization of the dipeptide by passage through an ion exchange resin yielded
2q.

In Examples 96-108, reference is made to the
following compounds

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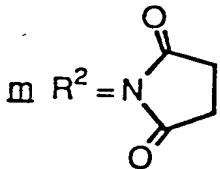
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- 2a $\text{R}^2 = \text{NHCH}_2\text{CH}_3$
b $\text{R}^2 = \text{NHNHCO}_2\text{CH}_2\text{Ph}$
c $\text{R}^2 = \text{NH}(\text{OCH}_3)$
d $\text{R}^2 = \text{N}(\text{CH}_3)\text{OCH}_3$
e $\text{R}^2 = \text{NHC(O)OCH}_3$
f $\text{R}^2 = \text{NHC(O)OPh}$
g $\text{R}^2 = \text{NHC(O)NHCH}_3$
h $\text{R}^2 = \text{NHC(O)NHPH}$
i $\text{R}^2 = \text{NHC(O)NHS(O}_2\text{)Ph}$
j $\text{R}^2 = \text{NHC(S)NHCH}_3$
k $\text{R}^2 = \text{NHC(S)NHPH}$
l $\text{R}^2 = \text{NHC(O)Ph(2'CO}_2\text{H)}$

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- m $\text{R}^2 = \text{NHC(O)CH}_2\text{NHC(O)OCH}_2\text{Ph}$
n $\text{R}^2 = \text{NHCH}_2\text{C(O)OCH}_2\text{CH}_3$
o $\text{R}^2 = \text{NHCH}_2\text{C(O)OCH}_2\text{Ph}$
p $\text{R}^2 = \text{NH}_2\text{CH}_2\text{CO}_2^-$
q $\text{R}^2 = \text{NH}_2$
r $\text{R}^2 = \text{Br}$
s $\text{R}^2 = \text{N}(\text{CH}_3)_3, \text{BF}_4^-$
t $\text{R}^2 = \text{NHC(O)CH}_3$
u $\text{R}^2 = \text{NHC(O)CF}_3$

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Example 96

1 *Chemistry - Synthesis of Methyl[acetamido(benzylcarbamoyl)methyl]carbamate (2e)*. Methyl chloroformate (0.33 g, 3.35 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) and Et₃N (0.39 g, 3.80 mmol) in THF (75 mL), and then the
5 reaction mixture was stirred at 55-60 °C (2 h). The Et₃N·HCl that precipitated was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was triturated with EtOAc (20 mL), and the remaining white solid (0.55 g, 62%) was filtered and recrystallized from EtOH: mp 202-204 °C (d); R_f 0.53 (10%
10 MeOH/CHCl₃); IR (KBr) 3260, 1650, 1500, 1440, 1360, 780, 690 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.86 (s, C(O)CH₃), 3.54 (s, OCH₃), 4.27 (d, J = 5.6 Hz, CH₂), 5.56 (t, J =
15 7.8 Hz, CH), 7.18-7.32 (m, 5PhH), 7.70 (br s, NHC(O)OCH₃), 8.40 (d, J = 7.8 Hz,
NH), 8.51 (t, J = 5.6 Hz, NH); ¹³C NMR (DMSO-d₆) 22.38 (C(O)CH₃), 42.29 (CH₂),
51.46 (OCH₃), 58.57 (CH), 126.52 (C_{4'}), 126.98 (2C_{2'} or 2C_{3'}), 127.99 (2C_{2'} or 2C_{3'}),
139.03 (C_{1'}), 167.83 (C(O)NH), 169.33 (C(O)CH₃) ppm, the carbamate carbonyl
signal was not detected. Mass spectrum (FD) 279 (M⁺).

20 Anal. Calcd for C₁₃H₁₇N₃O₄: C, 55.91; H, 6.14; N, 15.05. Found: C, 56.16;
H, 6.10; N, 14.89.

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VSq

Example 97

1 *Synthesis of Phenyl[acetamido(benzylcarbamoyl)methyl]carbamate (2f).*

Compound 2r (0.80 g, 3.62 mmol) was dissolved in warm THF (75 mL), and then Et₃N (0.44 g, 4.35 mmol), and phenyl chloroformate (0.62 g, 3.98 mmol) were added. The reaction mixture was stirred at 45-50 °C (2 h), and the volatile materials were removed *in vacuo*. The residue was triturated with EtOAc (20 mL) and the remaining white solid material (0.80 g, 65%) was filtered, washed with H₂O (10 mL), and then recrystallized from MeOH: mp 201-203 °C; R_f 0.38 (5% MeOH/CHCl₃); IR (KBr) 3400 (br), 3240, 1700, 1630, 1500, 1460, 1320, 1200, 740, 670 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, C(O)CH₃), 4.29-4.35 (m, CH₂), 5.66 (t, J = 7.6 Hz, CH), 7.08-7.42 (m, 10ArH), 8.43 (d, J = 7.6 Hz, NH), 8.58 (d, J = 7.6 Hz, NH), 8.67 (t, J = 5.0 Hz, NII); ¹³C NMR (DMSO-d₆) 22.58 (C(O)CH₃), 42.51 (CH₂), 58.69 (CH), 121.70 (2C₂), 125.18 (C₄), 126.76 (C_{4'}), 127.19 (2C_{2'} or 2C_{3'}), 128.21 (2C_{2'} or 2C_{3'}), 129.30 (2C₃), 139.14 (C_{1'}), 150.91 (C₁), 167.73 (C(O)NH), 169.75 (C(O)CH₃) ppm; the signal for the carbamate carbonyl was not detected. Mass spectrum (FD) 341 (M⁺).

20 Anal. Calcd for C₁₈H₁₉N₃O₄: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.06; H, 5.64; N, 12.12.

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Example 98

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylurea (2g).*
Methyl isocyanate (0.20 g, 3.48 mmol) was added to a solution of 2r (0.70 g, 3.16
mmol) in THF (75 mL), and then the reaction was stirred at 45-50 °C (2 h). The
5 white solid (0.80 g, 91%) that separated out was filtered and recrystallized from
MeOH to give 2g: mp 229-230 °C (d); R_f 0.25 (10% MeOH/CHCl₃); IR (KBr) 3200,
3060, 1630, 1500 (br), 1350, 1300, 740, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.82 (s,
C(O)CH₃), 2.54 (d, J = 4.5 Hz, NHCH₃), 4.26 (d, J = 5.8 Hz, CH₂), 5.59 (t, J = 7.8 Hz,
10 CH), 6.19 (d, J = 4.5 Hz, NHCH₃), 6.52 (d, J = 7.8 Hz, NHC(O)NHCH₃), 7.20-7.31 (m,
5PhH), 8.38 (t, J = 5.8 Hz, NH), 8.46 (d, J = 7.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.36
(C(O)CH₃), 26.03 (NHCH₃), 42.19 (CH₂), 57.92 (CH), 126.54 (C_{4'}), 126.93 (2C_{2'} or
2C_{3'}), 128.06 (2C_{2'} or 2C_{3'}), 139.16 (C_{1'}), 157.30 (NHC(O)NH), 168.89 (C(O)NH),
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169.37 (C(O)CH₃) ppm; mass spectrum (FD) 279 (M⁺⁺1).

Anal. Calcd for C₁₃H₁₈N₄O₃: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.31;
H, 6.41; N, 20.12.

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Example 99

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylurea (2h).*

Phenyl isocyanate (0.42 g, 3.5 mmol) was added to a solution of *2r* (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 45-50 °C (2 h). The 5 white solid (0.95 g, 89%) that precipitated. was filtered and dried: mp 242-244 °C (d); R_f 0.30 (5% MeOH/CHCl₃); IR (KBr) 3200 (br), 1600 (br), 1430 (br), 1300, 880, 700 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.86 (s, C(O)CH₃), 4.30 (d, J = 5.9 Hz, CH₂), 5.67 (t, J = 7.6 Hz, CH), 6.86-6.93 (m, 2ArH), 7.20-7.32 (m, NH, 5PhH, 1ArH), 7.37-7.40 (m, 10 2ArH), 8.56 (t, J = 5.9 Hz, NH), 8.68 (d, J = 7.6 Hz, NH), 8.89 (s, NH); ¹³C NMR (DMSO-d₆) 22.38 (C(O)CH₃), 42.29 (CH₂), 57.59 (CH), 117.61 (2C₂), 121.37 (C₄), 126.57 (C_{4'}), 126.95 (2C_{2'} or 2C_{3'}), 128.07 (2C_{2'} or 2C_{3'}), 128.62 (2C₃), 139.12 (C₁ or C_{1'}), 139.98 (C₁ or C_{1'}), 153.98 (NHC(O)NH), 168.55 (C(O)NH), 169.58 (C(O)CH₃) ppm; mass spectrum (FD) 340 (M⁺).

Anal. Calcd for C₁₈H₂₀N₄O₃: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.22; H, 5.92; N, 16.20.

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Example 100

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-benzenesulfonylurea (2i).* Benzenesulfonyl isocyanate (0.64 g, 3.48 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 50-55 °C
5 (22 h). The white solid (0.84 g, 66%) that separated on cooling was filtered and dried: mp 188-191 °C (d); R_f 0.11 (10% MeOH/CHCl₃); IR (KBr) 3250, 1630 (br), 1500 (br), 1460, 1330, 870, 700 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.80 (s, C(O)CH₃), 4.24 (d, J = 5.7 Hz, CH₂), 5.47 (t, J = 7.7 Hz, CH), 7.18-7.30 (m, 5PhH, NH), 7.57-7.71 (m, 3ArH),
10 7.89-7.92 (d, J = 7.5 Hz, 2ArH), 8.54 (t, J = 5.7 Hz, NH), 8.70 (d, J = 7.7 Hz, NH),
15 10.80 (s, NH); ¹³C NMR (DMSO-d₆) 22.29 (C(O)CH₃), 42.30 (CH₂), 57.14 (CH), 126.58 (C_{4'}), 126.89 (2C₂), 127.12 (2C_{2'} or 2C_{3'}), 128.05 (2C_{2'} or 2C_{3'}), 128.96 (2C₃), 133.25 (C₄), 138.88 (C₁ or C_{1'}), 139.87 (C₁ or C_{1'}), 150.36 (NHC(O)NH), 167.55 (C(O)NH),
169.55 (C(O)CH₃) ppm; mass spectrum (FD) 405 (M⁺⁺¹).

Anal. Calcd for C₁₈H₂₀N₄O₅S: C, 53.46; H, 4.98; N, 13.85. Found: C, 53.23;
H, 5.04; N, 13.62.

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Example 101

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylthiourea (2j).*

A solution of 2r (0.50 g, 2.26 mmol) and methyl isothiocyanate (0.20 g, 2.27 mmol) in THF (75 mL) was heated to reflux (4 h), and then the volatile materials were
5 removed *in vacuo*. The residue was recrystallized from absolute EtOH to give 2j as
a white solid (0.22 g, 33%): mp 162-163 °C (d); R_f 0.45 (10% MeOH/CHCl₃); IR (KBr)
3400 (br), 3220 (br), 1620, 1500, 1430, 1340, 740 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.83 (s,
C(O)CH₃), 2.85 (br s, NHCH₃), 4.27 (d, J = 5.8 Hz, CH₂), 6.10 (br s, CH), 7.17-7.30
10 (m, 5PhH), 7.80 (br s, NH), 7.96 (br s, NH), 8.44 (br s, NH), 8.72 (s, NH); ¹³C NMR
(DMSO-d₆) 22.39 (C(O)CH₃), 30.92 (NHCH₃), 42.45 (CH₂), 61.33 (CH), 126.68 (C_{4'}),
127.06 (2C_{2'} or 2C_{3'}), 128.16 (2C_{2'} or 2C_{3'}), 139.15 (C_{1'}), 168.17 (C(O)NH), 170.03
15 (C(O)CH₃) ppm, the signal for the thiocarbonyl carbon group was not detected.
Mass spectrum (FD) 294 (M⁺).

Anal. Calcd for C₁₃H₁₈N₄O₂S: C, 53.04; H, 6.16; N, 19.03. Found: C, 53.16;
H, 6.31; N, 18.89.

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Example 102

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylthiourea (2k)*

A solution of 2r (0.70 g, 3.16 mmol) and phenyl isothiocyanate (0.47 g, 3.48 mmol) in THF (75 mL) was heated to reflux (3 h), and then the volatile materials were
5 removed *in vacuo*. The residue was triturated with EtOH (15 mL), and the white solid material (0.70 g, 62%) that remained was filtered and recrystallized from absolute EtOH: mp 196-197 °C (d); R_f 0.65 (10% MeOH/CHCl₃); IR (KBr) 3400 (br), 3240 (br), 1620, 1470 (br), 1330, 750, 670 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.89 (s, 10 C(O)CH₃), 4.32 (d, J = 5.8 Hz, CH₂), 5.24 (t, J = 6.9 Hz, CH), 7.09-7.43 (m, 3ArH, 5PhH), 7.52-7.55 (m, 2ArH), 8.13 (d, J = 6.9 Hz, NH), 8.55 (br s, NH), 8.85 (br s, NH), 10.11 (s, NH); ¹³C NMR (DMSO-d₆) 22.22 (C(O)CH₃), 42.36 (CH₂), 61.18 (CH), 122.76 (2C₂), 124.29 (C₄), 126.53 (C_{4'}), 126.90 (2C_{2'} or 2C_{3'}), 128.00 (2C_{2'} or 2C_{3'}),
15 128.40 (2C₃), 138.94 (C₁ or C_{1'}), 139.01 (C₁ or C_{1'}), 167.82 (C(O)NH), 169.98 (C(O)CH₃), 180.02 (C(S)) ppm; mass spectrum (FD) 356 (M⁺).

Anal. Calcd for C₁₈H₂₀N₄O₂S: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.43; H, 5.70; N, 15.62.

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Example 103

1 *Synthesis of N-[Acetamido(benzylcarbamoyl)methyl]phthalamic acid (2I).*

To a warm pyridine solution (7.0 mL) containing 2r (0.63 g, 2.83 mmol), phthalic anhydride (0.43 g, 2.87 mmol) was added, and the reaction was stirred at 50-55 °C
5 (5 h). Pyridine was removed by distillation *in vacuo* and the residue was treated with H₂O (20 mL). The aqueous mixture was extracted with EtOAc (2 x 20 mL) and then acidified with aqueous 1 N HCl solution. The white solid (0.70 g, 70%) that precipitated was filtered, washed with H₂O (10 mL), and dried: mp
10 186-188 °C; ¹H NMR (DMSO-d₆) δ 1.90 (s, C(O)CH₃), 4.36 (d, *J* = 6.0 Hz, CH₂), 5.92 (t, *J* = 7.2 Hz, C_{II}), 7.20-7.31 (m, 5PhH), 7.43 (d, *J* = 7.3 Hz, C_{6II}), 7.50-7.63 (m, C₄H, C_{5II}), 7.82 (d, *J* = 7.3 Hz, C_{3II}), 8.41-8.48 (m, 2NII), 9.01 (d, *J* = 7.2 Hz, NH), 13.30 (br s, CO₂H); ¹³C NMR (DMSO-d₆) 22.46 (C(O)CH₃), 42.39 (CH₂), 57.44 (CH), 126.57, 126.92, 127.81, 128.09, 128.72, 129.36, 129.85, 131.49, 137.78, 138.99 (ArC, PhC), 15 167.85, 167.93, 168.48, 169.47 (C(O)) ppm; mass spectrum (FD) 370 (M⁺⁺1).

Anal. Calcd for C₁₉H₁₉N₃O₅: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.63;
20 H, 5.05; N, 11.16.

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Example 104

1 *Synthesis of 2-Acetamido-N-benzyl-2-(N-succinimidyl)acetamide (2m).* A
cooled (-78 °C) THF solution (150 mL) of 2s² (prepared from 2-acetamido-N-benzyl-
2-ethoxyacetamide^{4,5} (2.00 g, 8.0 mmol) and BBr₃ (2.51 g, 10.05 mmol)) was added
5 slowly into a cooled (-78 °C) THF suspension (50 mL) of sodium succinimide (3.06
g, 25.25 mmol). The reaction mixture was stirred at -78 °C (30 min) and at
room temperature (90 min), and then treated with a 10% aqueous citric acid
10 solution (50 mL). The resulting solution was neutralized with a saturated
aqueous NaHCO₃ solution, and the reaction mixture extracted with EtOAc (3 × 100
mL). The combined extracts were dried (Na₂SO₄), and the volatile materials were
removed by distillation *in vacuo*. The residue was purified by flash column
15 chromatography on SiO₂ gel (6% MeOH/CHCl₃) to give 1.10 g (45%) of 2m: mp 181-
183 °C (recrystallized from EtOH); R_f 0.26 (6% MeOH/CHCl₃); IR (KBr) 3340 (br),
1620 (br), 1480 (br), 1340, 780, 670 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.90 (s, C(O)CH₃),
2.67 (s, CH₂CH₂), 4.23-4.36 (m, CH₂), 6.31 (d, J = 9.0 Hz, CH), 7.17-7.35 (m, 5 PhH),
20 8.63 (t, J = 5.9 Hz, NH), 8.72 (d, J = 9.0 Hz, NH); ¹³C NMR (DMSO-d₆) 22.36
(C(O)CH₃), 27.99 (s, CH₂CH₂), 42.59 (CH₂), 55.19 (CH), 126.63 (C_{4'}), 126.96 (2C_{2'} or
2C_{3'}), 128.08 (2C_{2'} or 2C_{3'}), 138.91 (C_{1'}), 165.41 (C(O)NH), 169.86 (C(O)CH₃), 176.33
(C(O)CH₂CH₂C(O)) ppm; mass spectrum (FAB) 304 (M⁺+1, 17), 163 (12), 155 (48),
25 152 (51), 135 (68), 119 (100).

Anal. Calcd for C₁₅H₁₇N₃O₄: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.63;
H, 5.70; N, 13.66.

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Example 105

1 Synthesis of Benzyl N-[Acetamido(benzylcarbamoyl)methyl]malonamate (2n). 4-Methylmorpholine (0.35 g, 3.56 mmol) was added to a solution of N-CBZ-glycine (0.74 g, 3.55 mmol) in THF (75 mL) at -10 to -15 °C. The solution was 5 stirred (5 min), and then isobutylchlorosformate (0.49 g, 3.55 mmol) was added and the mixture was stirred for an additional 20 min. A cooled (-10 °C) solution of 2r (0.79 g, 3.55 mmol) in THF (125 mL) was then added slowly (30 min). The reaction mixture was stirred at this temperature (2 h) and then at room temperature (2 h).
10 The insoluble materials were filtered and the filtrate was concentrated *in vacuo*. The residue was triturated with EtOAc (20 mL) and the white solid (0.60 g) that remained was filtered, washed with H₂O and dried to give 2n. The initial insoluble material on trituration with H₂O gave an additional 0.40 g of 2n to give a
15 combined yield of 1.00 g (68%); mp 177-179 °C (recrystallized from EtOH); R_F 0.46 (10% MeOH/CHCl₃); IR (KBr) 3400 (br), 3260, 1640 (br), 1540 (br), 1480, 1450, 1370, 760, 690 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.86 (s, C(O)CH₃), 3.60-3.77 (m, C(O)CH₂NH), 4.28 (d, J = 5.8 Hz, CH₂), 5.01 (s, OCH₂Ph), 5.79 (t, J = 7.7 Hz, CH), 7.18-7.34 (m, 5
20 PhH, 5 ArH), 7.49 (t, J = 5.8 Hz, NH), 8.43-8.55 (m, 3 × NH); ¹³C NMR (DMSO-d₆) 22.36 (C(O)CH₃), 42.28 (CH₂), 43.39 (C(O)CH₂NH), 56.77 (CH), 65.42 (OCH₂Ph), 126.55 (2C), 126.94 (2C), 127.54, 127.66, 128.04 (2C), 128.22 (2C), 136.89, 138.96 (ArC, PhC), 156.40 (NHC(O)OCH₂Ph), 167.86 (NHC(O)CH₂), 168.96 (C(O)NH), 169.30
25 (C(O)CH₃) ppm; mass spectrum (FD) 413 (M⁺⁺¹, 100), 278 (75).

Anal. Calcd for C₂₁H₂₄N₄O₅: C, 61.16; H, 5.87; N, 13.58. Found: C, 60.90; H, 5.77; N, 13.35.

Example 106

1 *Synthesis of Ethyl N-[Acetamido(benzylcarbamoyl)methyl]glycinate (2o).* A
methanolic solution (70 mL) containing 2t (1.50 g, 4.28 mmol) and ethyl glycinate
(prepared from ethyl glycinate hydrochloride (3.10 g, 22.2 mmol), NaOMe (1.17 g,
5 21.74 mmol)) was heated to reflux (2h). The reaction was concentrated *in vacuo* to
give an oily residue that was purified by flash column chromatography on SiO₂
gel (5% MeOH/CHCl₃) to give 0.60 g (46%) of 2o: mp 125-127 °C (recrystallized from
EtOAc); R_f 0.43 (5% MeOH/CHCl₃); IR (KBr) 3400 (br), 3200, 1710, 1600, 1500, 1430,
10 1350, 740, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.17 (t, J = 7.1 Hz, OCH₂CH₃), 1.86 (s,
C(O)CH₃), 2.65-2.74 (m, NHCH₂C(O)), 3.26-3.33 (m, NHCH₂C(O)), 4.07 (q, J = 7.1
Hz, OCH₂CH₃), 4.28 (d, J = 5.8 Hz, CH₂), 5.01 (t, J = 8.2 Hz, CH), 7.19-7.35 (m, 5
PhH), 8.25 (d, J = 8.2 Hz, NH), 8.58 (t, J = 5.8 Hz, NH); ¹³C NMR (DMSO-d₆) 13.98
15 (OCH₂CH₃), 22.46 (C(O)CH₃), 42.13 (CH₂), 46.22 (NHCH₂C(O)), 60.07 (OCH₂CH₃),
63.96 (CH), 126.67 (C_{4'}), 127.09 (2C_{2'} or 2C_{3'}), 128.13 (2C_{2'} or 2C_{3'}), 139.07 (C_{1'}),
169.07 (C(O)NH), 170.09 (C(O)CH₃), 171.56 (C(O)OCH₂CH₃) ppm; mass spectrum
(FD) 342 (M⁺).
20 Anal. Calcd for C₁₅H₂₁N₃O₄: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.83;
H, 7.00; N, 13.73.

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Example 107

1 *Synthesis of Benzyl N-[Acetamido(benzylcarbamoyl)methyl]glycinate (2p).*

A suspension of benzyl glycinate hydrochloride (5.00 g, 24.8 mmol) in THF (400 mL) containing Et₃N (4.90 g, 48.5 mmol) was stirred (4 h) at room temperature.

5 The reaction mixture was cooled (-78 °C) and then a cooled (-78 °C) THF solution (150 mL) of 2s (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and BBr₃ (1 M in CH₂Cl₂, 20.0 mL, 20.0 mmol)) was added (30 min). The reaction mixture was stirred at -78 °C (30 min) and then at room temperature
10 (16 h). The insoluble materials were filtered, the filtrate concentrated *in vacuo*, and the residue was purified by flash column chromatography on SiO₂ gel (3% MeOH/CHCl₃) to give 1.56 g (26%) of 2p as a white solid: mp 133-135 °C (recrystallized from EtOH); R_f 0.36 (3% MeOH/CHCl₃); IR (KBr) 3400, 3220, 1710, 1620, 1510, 1440, 1350, 740, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.85 (s, C(O)CH₃), 2.71-2.82 (m, NHCH₂C(O)), 3.39 (d, J = 6.1 Hz, NHCHHC(O)), 3.40 (d, J = 6.1 Hz, NHCHHC(O)), 4.27 (d, J = 6.1 Hz, CH₂), 5.02 (t, J = 8.2 Hz, CH), 5.11 (s, OCH₂Ph),
15 7.19-7.36 (m, 5 PhH, 5 ArH), 8.24 (d, J = 8.2 Hz, NH), 8.57 (t, J = 6.1 Hz, NH); ¹³C NMR (DMSO-d₆) 22.42 (C(O)CH₃), 42.11 (CH₂), 46.22 (NHCH₂C(O)), 63.94 (CH), 65.53 (OCH₂Ph), 126.62, 127.05 (2C), 127.80 (2C), 127.91, 128.08 (2C), 128.29 (2C), 135.87, 139.02 (ArC, PhC), 169.01 (C(O)NH), 170.06 (C(O)CH₃), 171.45 (C(O)OCH₂Ph) ppm; mass spectrum (FD) 370 (M⁺⁺¹).

Anal. Calcd for C₂₀H₂₃N₃O₄: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.15; H, 6.53; N, 11.31.

Example 108

1 *Synthesis of N-[Acetamido(benzylcarbamoyl)methyl]glycine (2g).* A solution
of methyl N-[acetamido(benzylcarbamoyl)methyl]glycinate (0.60 g, 2.05 mmol) and
KOH (0.30 g, 5.36 mmol) in 90% aqueous EtOH (50 mL) was stirred at room
5 temperature (48 h). The volatile materials were then removed *in vacuo*, and the
residue dissolved in H₂O (10 mL). The aqueous solution was extracted with EtOAc
(2 x 20 mL), and the aqueous layer was acidified to pH ~2.0 with aqueous 1 N HCl.
A column containing ion exchange resin Dowex 50X W4 was prepared using 10%
10 aqueous pyridine. The column was thoroughly washed with H₂O. The acidic
aqueous reaction solution was added to the top of the column, and the column was
eluted with H₂O (300 mL) or until the eluate was neutral. The column was then
eluted with 10% aqueous pyridine (400 mL). The aqueous pyridine fraction was
15 concentrated *in vacuo* to give a white solid, dried *in vacuo*, and then triturated
with absolute EtOH (7 mL). The insoluble materials that remained were filtered
and dried to give 0.29 g (50%) of 2g: mp 124-126 °C (d); IR (KBr) 3400, 3200, 1630,
1500, 1370, 690 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.84 (s, C(O)CH₃), 3.26 (s, CH₂C(O)),
20 4.29 (d, J = 5.7 Hz, CH₂), 4.98 (d, J = 8.2 Hz, CH), 7.21-7.33 (m, NH, 5 PhH), 8.39 (d,
J = 8.2 Hz, NH), 8.47 (t, J = 5.7 Hz, NH); ¹³C NMR (DMSO-d₆) 22.41 (C(O)CH₃),
41.98 (CH₂), 47.48 (CH₂C(O)), 64.08 (CH), 126.75 (C_{4'}), 127.21 (2C_{2'} or 2C_{3'}), 128.24
25 (2C_{2'} or 2C_{3'}), 139.23 (C_{1'}), 169.91 (C(O)NH), 170.02 (C(O)CH₃), 170.20 (CH₂C(O))
ppm.

Anal. Calcd for C₁₃H₁₇N₃O₄: C, 55.91; H, 6.13; N, 15.04. Found: C, 55.68;
H, 6.06; N, 14.74.

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Example 109

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole)acetamide.* A cooled (-78 °C)
THF solution (225 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from
2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr_3 (1 M CH_2Cl_2
5 solution, 8.8 mL, 8.8 mmol)) was added under N_2 to a cooled (-78 °C) suspension of
potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was
stirred at -78 °C (1 h) and then at room temperature (1 h), and then treated with
H₂O (10 mL) and acidified ("pH" 4.0) with 5% citric acid. The reaction was made
10 basic with aqueous saturated Na₂CO₃ solution, and the aqueous mixture was
extracted with EtOAc (2 x 250 mL) and the combined organic layers were dried
(Na₂SO₄). The volatile materials were removed *in vacuo* and the residue was
15 purified by flash column chromatography on SiO₂ gel using 3% MeOH/CHCl₃ as
the eluant to give 0.40 g (18%) of the desired product. The compound X was
purified by recrystallization from EtOH: mp 182-184 °C; R_f 0.44 (4%
MeOH/CHCl₃); IR (KBr) 3400, 3280, 1630, 1520, 1370, 740, 720 cm⁻¹; ¹H NMR
(DMSO-d₆) δ 1.91 (s, C(O)CH₃), 4.30 (d, J = 5.5 Hz, CH₂), 6.01 (s, 2 x C₃H), 6.38 (d, J
20 = 8.7 Hz, CHI), 6.85 (s, 2 x C₂H), 7.11-7.35 (m, 5PhH), 8.96 (t, J = 5.5 Hz, NII), 9.14 (d,
J = 8.7 Hz, NH); ¹³C NMR (DMSO-d₆) 22.22 (C(O)CH₃), 42.15 (CH₂), 62.86 (CH),
107.79 (2C₃), 119.19 (2C₂), 126.76 (C_{4'}), 127.01 (2C_{2'} or 2C_{3'}), 128.11 (2C_{2'} or 2C_{3'}),
25 138.34 (C_{1'}), 166.37 (C(O)NH), 169.41 (C(O)CH₃) ppm; mass spectrum, m/e (relative
intensity) 272 (M⁺⁺¹, 22), 271 (M⁺, 100).

Anal. Calcd for C₁₅H₁₇N₃O₂·0.2 H₂O: C, 65.53; H, 6.37; N, 15.28. Found: C,
65.80; H, 6.22; N, 15.13.

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Example 110

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole)acetamide.* To a cooled (-78 °C) solution (250 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.60 g, 14.4 mmol) and BBr_3 (1 M 5 CH_2Cl_2 solution, 15.8 mL, 15.8 mmol)), a THF solution (20 mL) of Et_3N (2.91 g, 28.8 mmol) was added; followed by the addition of THF solution (30 mL) of pyrazole (1.17 g, 17.28 mmol). The mixture was stirred at -78 °C (30 min) and room temperature (1 h). The insoluble materials were filtered and the solvents removed 10 *in vacuo*. The residue was purified by flash column chromatography on SiO_2 gel using 4% MeOH/CHCl₃ as the eluant to give 0.80 g (22%) of the desired product. The compound X was recrystallized from EtOAc as a white solid: mp 158-160 °C; R_f 0.51 (6% MeOH/CHCl₃); IR (KBr) 3400, 3180, 1650, 1530, 1470, 1370, 1350, 740, 700 15 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.93 (s, C(O)CH₃), 4.29 (d, *J* = 5.8 Hz, CH₂), 6.26 (s, C₄H), 6.57 (d, *J* = 8.8 Hz, CH), 7.15-7.33 (m, 5PhH), 7.48 (br s, C₅H), 7.76 (br s, C₃H), 8.96 (t, *J* = 5.8 Hz, NH), 9.23 (d, *J* = 8.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.41 20 (C(O)CH₃), 42.40 (CH₂), 65.51 (CH), 105.37 (C₄), 126.87 (C_{4'}), 127.14 (2C_{2'} or 2C_{3'}), 128.25 (2C_{2'} or 2C_{3'}), 129.00 (C₅), 138.59 (C₃), 139.17 (C_{1'}), 165.68 (C(O)NH), 169.81 (C(O)CH₃) ppm; mass spectrum, m/e (relative intensity) 273 (M⁺+1, 11), 272 (M⁺, 2), 139 (83), 138 (100), 92 (37).

25 Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 5.96; N, 20.28.

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Example 111

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole)acetamide.* Using the
preceeding procedure, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0
mmol), BBr₃ (1 M CH₂Cl₂ solution, 8.8 mL, 8.8 mmol), Et₃N (1.62 g, 1.60 mmol),
5 and imidazole (0.60 g, 8.8 mmol) gave 0.60 g (30%) of the desired product.
Compound X was recrystallized from ethyl acetate/hexane as a beige colored
solid: mp 146-148 °C; R_f 0. (7% MeOH/CHCl₃); IR (KBr) 3400 (br), 1640, 1560, 1480,
1360, 720, 670 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.85 (s, C(O)CH₃), 4.30 (br s, CH₂), 6.53
10 (d, J = 8.0 Hz, CH), 6.89 (s, C₅H), 7.12-7.33 (m, C₄H, 5PhH), 7.69 (s, C₂H), 9.06 (br s,
NH), 9.29 (d, J = 8.0 Hz, NH); ¹³C NMR (DMSO-d₆) 22.28 (C(O)CH₃), 42.36 (CH₂),
15 61.18 (CH), 117.56 (C₅), 126.92 (C₄), 127.16 (2C_{2'} or 2C_{3'}), 128.19 (C₄), 128.26 (2C_{2'} or
2C_{3'}), 136.21 (C₂), 138.27 (C_{1'}), 165.72 (C(O)NH), 169.77 (C(O)CH₃) ppm; mass
spectrum, FD (relative intensity) 274 (M⁺+2, 12), 273 (M⁺+1, 77), 272 (100), 205 (34),
274 (18).

Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;
20 H, 6.09; N, 20.32.

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Example 112

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole))acetamide.* Using 2-
acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), BBr_3 (1 M CH_2Cl_2
solution, 17.6 mL, 17.6 mmol), Et_3N (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g,
5 20.8 mmol), 1.20 g (28%) of the desired product was obtained. Compound X was
recrystallized from EtOAc as an amorphous white solid: mp 146-148 °C; R_f 0.48
(6% MeOH/CHCl₃); IR (KBr) 3400, 1660, 1470, 1370, 830 cm^{-1} ; ¹H NMR (DMSO-d₆) δ
1.85 (s, C(O)CH₃), 4.32 (br s, CH₂), 6.70 (d, J = 7.8 Hz, CH), 7.21-7.29 (m, 5PhH),
10 8.01 (s, C₃H), 8.57 (s, C₅H), 9.04 (br s, NH), 9.39 (d, J = 7.8 Hz, NH); ¹³C NMR
(DMSO-d₆) 22.39 (C(O)CH₃), 42.59 (CH₂), 65.02 (CH), 126.97 (C_{4'}), 127.25 (2C_{2'} or
2C_{3'}), 128.32 (2C_{2'} or 2C_{3'}), 138.47 (C_{1'}), 143.93 (C₅), 151.50 (C₃), 164.77 (C(O)NH),
15 170.23 (C(O)CH₃) ppm; mass spectrum, FD (relative intensity) 274 ($M^{+}+1$, 100), 273
(11), 205 (19), 204 (13), 140 (67), 139 (31).

Anal. Calcd for C₁₃H₁₅N₅O₂: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37;
H, 5.66; N, 25.38.

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Example 113

1 *Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole))acetamide.* Making use of
2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr_3 (1 M CH_2Cl_2
solution, 13.2 mL, 13.2 mmol), Et_3N (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6
5 mmol), 0.90 g (27%) of the desired product was obtained as a white solid. The
compound X was recrystallized from EtOH : mp 169-171 °C; R_f 0.22 (4%
 $\text{MeOH}/\text{CHCl}_3$); IR (KBr) 3300 (br), 1660, 1510, 1360, 870, 740 cm^{-1} ; ^1H NMR (DMSO-
10 d_6) δ 1.97 (s, $\text{C}(\text{O})\text{CH}_3$), 4.25-4.40 (m, CH_2), 7.05 (d, $J = 8.4$ Hz, CH), 7.21-7.38 (m,
 5PhH), 9.23 (t, $J = 5.5$ Hz, NH), 9.44 (s, C_5H), 9.69 (d, $J = 8.4$ Hz, NH); ^{13}C NMR
15 (DMSO- d_6) 22.38 ($\text{C}(\text{O})\text{CH}_3$), 42.78 (CH_2), 63.62 (CH), 127.10 (C_4'), 127.39 (2 C_2' or
2 C_3'), 128.38 (2 C_2' or 2 C_3'), 138.26 (C_1'), 143.67 (C_5), 163.88 ($\text{C}(\text{O})\text{NH}$), 170.62
($\text{C}(\text{O})\text{CH}_3$) ppm; mass spectrum, FD (relative intensity) 275 (M^+ , 79), 273 (14), 206
(100), 205 (50).

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_6\text{O}_2$: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75;
H, 5.33; N, 30.64.

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Example 114

1 *Synthesis of α -Acetamido-N-benzyl-1-(dimethylsulfamoyl)imidazole-4-acetamide.* To a cooled (-78 °C) THF solution (150 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr₃ (1 M solution in CH₂Cl₂, 9.0 mL, 9.0 mmol)) was added Et₃N (1.62 g, 16.0 mmol), and then a THF solution of the 2-lithio salt of N,N-dimethylimidazole-1-sulfonamide (generated by the addition of n-BuLi (2.5 M in hexane, 3.9 mL, 9.68 mmol) into a cooled (-78 °C) THF solution (25 mL) of N,N-dimethylimidazole-1-sulfonamide (1.54 g, 8.8 mmol)) was added during a 15 min interval. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (45 min). A saturated aqueous NH₄Cl solution (50 mL) and H₂O (50 mL) were then successively added to the reaction, and the aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na₂SO₄), and the volatile materials were removed by distillation *in vacuo*. The residue was purified by flash column chromatography on SiO₂ gel (4% MeOH/CHCl₃) to give 0.50 g (17%) of the desired product: mp 145-147 °C (recrystallized from EtOAc/hexane); R_f 0.35 (4% MeOH/CHCl₃); IR (KBr) 3400, 1640, 1530, 1380, 720 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.96 (s, C(O)CH₃), 2.77 (s, N(CH₃)₂), 4.25 (dd, J = 6.0, 15.5 Hz, CHH), 4.34 (dd, J = 6.0, 15.5 Hz, CHH), 5.43 (d, J = 8.0, Hz, CH), 7.19-7.30 (m, 5 PhH), 7.40 (s, C₅H), 8.17 (s, C₂H), 8.42 (d, J = 8.0 Hz, NH), 8.67 (t, J = 6.0 Hz, NH); ¹³C NMR (DMSO-d₆) 22.42 (C(O)CH₃), 37.80 (N(CH₃)₂), 42.11 (CH₂), 51.40 (CH), 115.50 (C₅), 126.64 (C_{4'}), 126.94 (2C_{2'} or 2C_{3'}), 128.12 (2C_{2'} or 2C_{3'}), 136.70 (C₂), 139.17 (C_{1'}), 140.26 (C₄), 168.93 (C(O)NH), 169.09 (C(O)CH₃) ppm; mass spectrum (FD) 380 (M⁺⁺1, 34), 248 (13), 247 (100), 108 (64).

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Anal. Calcd for C₁₆H₂₁N₅O₄S: C, 50.65; H, 5.58; N, 17.87. Found: C, 51.92; H, 5.65; N, 18.09.

Example 115

Synthesis of α -Acetamido-N-benzyl-4-imidazole acetamide. A 75% aqueous EtOH (16 mL) solution of α -acetamido-N-benzyl-1-(N,N-dimethylsulfamido)imidazole-4-acetamide (0.85 g, 3.05 mmol) was acidified ("pH" ~1.5) with ethanolic HCl, and the solution was heated to reflux (8 h). The reaction was neutralized with a saturated aqueous NaHCO₃ solution and the EtOH-H₂O azeotrope removed by distillation *in vacuo*. The remaining aqueous layer was made basic ("pH" 10) with aqueous NaOH. The aqueous mixture was extracted with EtOAc (3 × 50 mL) and the combined extracts were dried (Na₂SO₄). The reaction was concentrated *in vacuo* to give 0.35 g (57%) of the desired product: mp 189-191 °C (d) (recrystallized from acetone); R_f 0.19 (10% MeOH/CHCl₃); IR (KBr) 3400, 3260, 1650, 1600, 1500, 1430, 1360, 1330, 730, 710 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.88 (s, C(O)CH₃), 4.28 (d, J = 5.9 Hz, CH₂), 5.38 (d, J = 6.8 Hz, CH), 5.38 (br s, C₅H), 7.15-7.30 (m, 5 PhH), 7.60 (s, C₂H), 8.26 (br s, NH), 8.53 (br s, NH), 12.01 (br s, NH) ppm; mass spectrum (FD) 273 (M⁺⁺1).

Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.59; H, 5.98; N, 20.37.

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Example 116

1 *Synthesis of α-Acetamido-N-benzyl-2-imidazole acetamide.*

Preparation of 1-diethoxymethyl-2-lithioimidazole. n-BuLi (2.5 M in hexane, 6.8 mL, 17.0 mmol) was added to a cooled (-46 °C) solution of 1-diethoxymethylimidazole (2.90 g, 17.06 mmol) in THF (45 mL) under N₂ atm. The 5 solution was stirred at -46 °C (15 min) to give the desired product.

Preparation of α-Acetamido-N-benzyl-2-imidazoleacetamide. The 2-lithio salt solution of 1-diethoxymethylimidazole was added dropwise (15 min) into a 10 cooled (-78 °C) THF solution (130 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr₃ (1 M in CH₂Cl₂, 10 mL, 10.0 mmol)). The reaction was stirred at -78 °C (1 h) and then quenched with a saturated aqueous NH₄Cl (50 mL) solution. The 15 mixture was stirred at room temperature (30 min), and made basic ("pH" 9.2) by adding aqueous K₂CO₃. The aqueous mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were dried (Na₂SO₄). The solvents were removed 20 *in vacuo* and the residue was purified by flash column chromatography on SiO₂ gel (2.5% MeOH/CHCl₃) to give 0.14 g (7%) of the desired product: mp 228-230 °C (recrystallized from EtOH); R_f 0.46 (10% MeOH/CHCl₃); IR (KBr) 3200 (br), 1610, 1500 (br), 1430, 1350, 740, 680 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.91 (s, C(O)CH₃), 4.29 (d, J = 5.6 Hz, CH₂), 5.51 (d, J = 7.7 Hz, CH), 6.85 (br s, C₄H), 7.05 (br s, C₅H), 7.18-7.30 (m, 5 PhH), 8.42 (d, J = 7.7 Hz, NH), 8.65 (t, J = 5.6 Hz, NH), 11.91 (br s, NH); ¹³C NMR (DMSO-d₆) 22.49 (C(O)CH₃), 42.21 (CH₂), 51.62 (CH), 126.60 (C_{4'}), 126.98 (2C_{2'} or 2C_{3'}), 127.21 (C₄), 128.09 (2C_{2'} or 2C_{3'}), 128.32 (C₅), 139.05 (C_{1'}), 143.74 (C₂), 30 168.12 (C(O)NH), 169.30 (C(O)CH₃) ppm; mass spectrum (FD) 273 (M⁺+1, 65), 272 (M⁺, 100).

Anal. Calcd for C₁₄H₁₆N₄O₂: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.56; H, 5.92; N, 20.37.

Example 117

1 *Synthesis of α -Acetamido-N-benzyl-5-(tetrazole)acetamide.* A mixture of 2-acetamido-N-benzyl-2-cyanoacetamide (1.00 g, 4.33 mmol), potassium azide (1.70 g, 20.96 mmol) and Et₃N·HCl (1.78 g, 13.0 mmol) in 1-methyl-2-pyrrolidinone (125 mL) was stirred at 110 °C (7 h). After cooling, aqueous concentrated HCl (1 mL) was added, and the reaction mixture was filtered. The solvent was removed *in vacuo*. The residue was dissolved in aqueous 1 N NaOH (20 mL), and then aqueous 1 N HCl (20 mL) was added. The precipitate was filtered to give 0.77 g
10 (65%) of the desired product. The compound X was recrystallized from EtOH: mp 236-238 °C; R_f 0.20 (30% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.94 (s, C(O)CH₃), 4.33 (d, J = 5.7 Hz, CH₂), 5.89 (d, J = 7.8 Hz, CHI), 7.18-7.33 (m, 5 PhH), 8.86 (d, J = 7.8 Hz, NH), 8.92 (t, J = 5.7 Hz, NH), 16.54 (br s, NH); ¹³C NMR (DMSO-d₆) 22.21
15 (C(O)CH₃), 42.37 (CH₂), 48.13 (CH), 126.67 (C_{4'}), 127.00 (2C_{2'} or 2C_{3'}), 128.05 (2C_{2'} or 2C_{3'}), 138.52 (C_{1'}), 166.18 (C(O)NH), 169.58 (C(O)CH₃) ppm; mass spectrum, FD (relative intensity) 275 (M⁺+1, 73), 274 (100). M_r (+CI) 274.119201 (calcd for C₁₂H₁₄N₆O₂: 274.117824).

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Example 118

1 *Synthesis of α-Acetamido-N-benzyl-3-(1,2,4-triazole)acetamide.* An
ethanolic solution (250 mL) of 2-acetamido-N-benzyl-2-cyanoacetamide (3.00 g, 13.0
mmol), formic hydrazide (1.60 g, 26.0 mmol) and K₂CO₃ (6.00 g, 2.90 mmol) was
5 heated at reflux (20h). The reaction mixture was allowed to cool, filtered, and
the solvent was removed *in vacuo*. The residue was purified by flash column
chromatography on SiO₂ gel using 13% MeOH/CHCl₃ as the eluant to give 1.40 g
(40%) of the desired product. The compound X was purified by recrystallization
10 from EtOH: mp 205-207 °C; R_f 0.35 (16% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.92
(s, C(O)CH₃), 4.30 (d, J = 5.7 Hz, CH₂), 5.62 (d, J = 7.8 Hz, CH), 7.18-7.32 (m, 5
PhH), 8.53 (s, C₅H), 8.56 (d, J = 7.8 Hz, NH), 8.71 (t, J = 5.7 Hz, NH), 13.98 (s, NH);
15 ¹³C NMR (DMSO-d₆) 22.48 (C(O)CH₃), 42.41 (CH₂), 51.30 (CH), 126.63 (C_{4'}), 127.08
(2C_{2'} or 2C_{3'}), 128.11 (2C_{2'} or 2C_{3'}), 139.05 (C_{1'}), 167.92 (C(O)NH), 169.32 (C(O)CH₃)
ppm; mass spectrum, FD (relative intensity) 274 (M⁺⁺¹, 100), 273 (66).

Anal. Calcd for C₁₃H₁₅N₅O₂: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.32;
H, 5.57; N, 25.53.

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Example 119

1 *Synthesis of α-Acetamido-N-benzyl-2-(carboxamide oxime)acetamide.* A suspension of NH₂OH·HCl (1.80 g, 25.9 mmol), K₂CO₃ (4.85 g, 35.0 mmol), 2-acetamido-N-benzyl-2-cyanoacetamide (2.00 g, 8.65 mmol) in absolute EtOH (150 mL) was heated at reflux (16 h). The reaction mixture was cooled, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on SiO₂ gel using 8% MeOH/CHCl₃ as the eluant to give 1.24 g (54%) of the desired product. The compound X was further purified by
10 recrystallization from ethyl acetate/hexane: mp 172-173 °C; R_f 0.40 (10% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.87 (s, C(O)CH₃), 4.27 (d, J = 6.0 Hz, CH₂), 4.88 (d, J = 8.4 Hz, CH), 5.37 (s, NH₂), 7.21-7.30 (m, 5 PhH), 8.21 (d, J = 8.4 Hz, NH), 8.48 (t, J = 6.0 Hz, NH), 9.28 (s, OH); ¹³C NMR (DMSO-d₆) 22.46 (C(O)CH₃), 42.15
15 (CH₂), 53.65 (CH), 126.60 (C_{4'}), 126.99 (2C_{2'} or 2C_{3'}), 128.108 (2C_{2'} or 2C_{3'}), 139.02 (C_{1'}), 149.63 (CNH₂), 167.88 (C(O)NH), 169.07 (C(O)CH₃) ppm; mass spectrum, FD (relative intensity) 265 (M⁺+1, 36), 264 (100).

Anal. Calcd for C₁₂H₁₆N₄O₃: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.81;
20 H, 6.01; N, 21.41.

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Example 120

1 *Synthesis of α-Acetamido-N-benzyl-2-(carboxamide oxime-(O-acetate))-acetamide.* To a stirred solution of α-acetamido-N-benzyl-2-(carboxamide oxime)acetamide (0.72 g, 7.25 mmol) in pyridine (8 mL), acetyl chloride (0.25 mL,
5 X mmol) was added dropwise. Upon addition of the acetyl chloride a small exotherm was detected (25 °C to 37 °C). The reaction mixture was stirred at room temperature (1 h). The solvent was then removed *in vacuo*, and the residue was dissolved in CH₂Cl₂ (100 mL). The solution was washed with an aqueous 0.5 N
10 HCl solution (20 mL). The organic phase was dried (Na₂SO₄), and the solvent was removed *in vacuo* to give 0.60 g (72%) of the desired product. The compound X was recrystallized from chloroform/hexane: mp 131-133 °C; R_f 0.35 (4%
15 MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.90 (s, C(O)CH₃), 2.06 (s, OC(O)CH₃), 4.29 (t,
J = 5.3 Hz, CH₂), 5.00 (d, J = 8.4 Hz, CH), 6.48 (br s, NH₂), 7.19-7.33 (m, 5 PhH), 8.29
20 (d, J = 8.4 Hz, NH), 8.66 (t, J = 5.3 Hz, NH); ¹³C NMR (DMSO-d₆) 19.86 (OC(O)CH₃),
22.77 (C(O)CH₃), 42.50 (CH₂), 53.45 (CH), 126.89 (C_{4'}), 127.28 (2C_{2'} or 2C_{3'}), 128.38
25 (2C_{2'} or 2C_{3'}), 139.00 (C_{1'}), 156.13 (CNH₂), 167.19 (C(O)NH), 168.49 (OC(O)CH₃),
169.55 (C(O)CH₃) ppm; mass spectrum, FD (relative intensity) 307 (M⁺⁺1, 100), 306
(43).

Anal. Calcd for C₁₄H₁₈N₄O₄: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.86;
25 H, 5.84; N, 18.19.

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Example 121

1 *Synthesis of α -Acetamido-N-benzyl-3-(1,2,4-oxadiazole)acetamide.* α -Acetamido-N-benzyl-2-(carboxamide oxime)acetamide (0.90 g, 3.4 mmol) was dissolved in trimethylorthosformate (10 mL) containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6 drops). The
5 solution was warmed to 55 °C (20 min), and then evaporated under reduced pressure to give a white-blue solid. The material was dissolved in MeOH and treated with norit, filtered, and evaporated under reduced pressure to furnish crude product (0.79 g, 85%). The compound was purified by recrystallization from
10 chloroform/hexane: mp 164-166 °C; R_f 0.37 (6% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.92 (s, C(O)CH₃), 4.31 (d, J = 6.0 Hz, CH₂), 5.82 (d, J = 8.4 Hz, CH), 7.15-7.34
15 (m, 5 PhH), 8.88 (d, J = 8.4 Hz, NH), 8.96 (t, J = 6.0 Hz, NH), 9.62 (s, C₅H); ¹³C NMR (DMSO-d₆) 22.22 (C(O)CH₃), 42.35 (CH₂), 49.44 (CH), 126.77 (C_{4'}), 127.06 (2C_{2'} or
2C_{3'}), 128.18 (2C_{2'} or 2C_{3'}), 138.70 (C_{1'}), 166.25 (C(O)NH), 166.74 (C₃), 167.24
(C(O)CH₃), 169.52 (C₅, CH) ppm; mass spectrum, FD (relative intensity) 275
(M⁺+1, 28), 274 (100).

20 Anal. Calcd for C₁₃H₁₄N₄O₃: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.65;
H, 5.01; N, 20.28.

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Example 122

1 *Synthesis of α-Acetamido-N-benzyl-2-(thioamide)acetamide.* 2-Acetamido-
N-benzyl-2-cyanoacetamide (4.00 g, 34.64 mmol) and O,O-diethyldithiophosphoric
acid (6.45 g, 34.64 mmol) were dissolved in a binary MeOH (80 mL)-EtOH (80 mL)
5 solution containing H₂O (0.32 mL) and heated at 70 °C (6 h), and then allowed to
remain at room temperature (13 h). The reaction mixture was filtered, and the
solvent was removed *in vacuo*. The residue was triturated with EtOAc to give 2.00
10 g (44%) of the desired compound. The thioamide was recrystallized from ethyl
acetate/hexane: mp 170-171 °C; R_f 0.51 (8% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ
1.93 (s, C(O)CH₃), 4.29 (d, J = 5.0 Hz, CH₂), 5.21 (d, J = 8.0 Hz, CH), 7.15-7.31 (m, 5
PhH), 8.03 (d, J = 8.0 Hz, NH), 8.69 (t, J = 5.0 Hz, NH), 9.27 (s, NH⁺), 9.91 (s,
15 NH⁺); ¹³C NMR (DMSO-d₆) 22.68 (C(O)CH₃), 42.24 (CH₂), 62.95 (CH), 126.63 (C_{4'}),
126.96 (2C_{2'} or 2C_{3'}), 128.087 (2C_{2'} or 2C_{3'}), 138.83 (C_{1'}), 166.42 (C(O)NH), 169.10
15 (C(O)CH₃), 200.28 (C(S)NH₂) ppm; mass spectrum, FD (relative intensity) 266
(M⁺⁺1, 42), 265 (100).

20 Anal. Calcd for C₁₂H₁₅N₃O₂S: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.44;
H, 5.74; N, 15.54.

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Example 123

1 *Synthesis of Ethyl 2-Acetamido-2-vinylacetate.* Vinyl magnesium bromide
 (10.9 mL, 1 N, 10.9 mmol) was slowly added to a cooled (-78 °C) solution of ethyl 2-
 acetamido-2-bromoacetate (1.10 g, 4.91 mmol) in THF (50 mL). The reaction was
5 stirred at -78 °C (2 h), and was then quenched with a 1 N citric acid solution (7.0
 mL). The mixture was allowed to warm to room temperature, and then the THF
 was removed *in vacuo*. The aqueous mixture was extracted with CHCl₃ (3 x 100
 mL), and the combined CHCl₃ extracts were dried (Na₂SO₄) and concentrated to
10 dryness. The residue was purified by flash chromatography using SiO₂ gel and
 2% MeOH/CHCl₃ as the eluant to give 0.50 g (60%) of the desired product as a light
 yellow colored oil: R_f 0.51 (4% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.17 (t, J = 7.1
 Hz, OCH₂CH₃), 1.88 (s, C(O)CH₃), 4.09 (d, J = 7.1 Hz, OCH₂CH₃), 4.80-4.86 (m, α-
15 CH), 5.22-5.35 (m, CH=CH₂), 5.82-5.92 (m, CH=CH₂), 8.47 (d, J = 7.4 Hz, NH); ¹³C
 NMR (DMSO-d₆) 13.96 (OCH₂CH₃), 22.12 (C(O)CH₃), 54.65 (α-CH), 60.71
 (OCH₂CH₃), 117.89 (CH=CH₂), 132.48 (CH=CH₂), 169.16 (C(O)CH₃), 170.26
 (C(O)NH) ppm.
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Example 124

1 *Synthesis of Vinyl Glycine.* A mixture of ethyl 2-acetamido-2-vinyl acetate (5.20 g, 30.40 mmol) and aqueous 6 N HCl (200 mL) was heated to reflux (2 h). The mixture was cooled to room temperature, and then extracted with CHCl₃ (3 x 100 mL). The aqueous solution which was dark brown in color was decolorized with norit (15 min) at 60 °C, and then the mixture was filtered, and the filtrate was concentrated to dryness to give aude vinyl glycine hydrochloride. The salt was dissolved in a minimum amount of H₂O and acidified to pH 2.0 with aqueous 1 N HCl. The solution was applied to an ion exchange resin (Dowex 50XW4, ammonium form) and eluted with H₂O until the eluate was neutral. The ion exchange column was then eluted with an aqueous 1 N NH₄OH solution (~500 mL). Removal of volatile materials from the NH₄OH eulate gave 1.80 g (60%) of vinyl glycine: mp 218-220 °C (d); ¹H NMR (D₂O) δ 4.09 (d, *J* = 7.2 Hz, α-CH), 5.28-5.35 (m, CH=CH₂), 5.80-5.87 (m, CH=CH₂).

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Example 125

1 *Synthesis of 2-Acetamido-2-vinylacetic acid.* Acetic anhydride (2.50 g, 24.50 mmol) was added slowly into a cooled (-10 °C) solution of vinyl glycine (2.20 g, 21.78 mmol) in AcOH (100 mL). The mixture was stirred at this temperature (30 min) and then at room temperature (3 h). The solution was concentrated repeatedly from H₂O. The residue was dissolved in absolute EtOH (200 mL) and then decolorized (norit, 60 °C), and filtered. The filtrate was concentrated *in vacuo*, and the residue was triturated with Et₂O to give 1.70 g (55%) of the desired product
5 as a low melting yellow solid: ¹H NMR (DMSO-d₆) δ 1.87 (s, C(O)CH₃), 4.75 (dd, *J* = 6.2, 7.5 Hz, α-CH), 5.13-5.27 (m, CH=CH₂), 5.84-5.96 (m, CH=CH₂), 8.24 (d, *J* = 7.5 Hz, NH).

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Example 126

Synthesis of 2-Acetamido-N-benzyl-2-vinylacetamide. 4-Methyl morpholine (0.71 g, 6.99 mmol) was added to a suspension of 2-acetamido-2-vinylacetic acid (1.00 g, 6.99 mmol) in THF (325 mL), and the mixture was stirred at room temperature (30 min). The reaction was cooled to -10 to -15 °C and then isobutylchloroformate (1.24 g, 9.08 mmol) was then added dropwise. After stirring (10 min), a solution of benzylamine (0.75 g, 6.99 mmol) in THF (25 mL) was added (15 min). The reaction mixture was allowed to warm to 0 °C. The insoluble material was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on SiO₂ gel using 3% MeOH/CHCl₃ as the eluant to give 1.00 g (62%) of the desired product: mp 136-138 °C (recrystallized from EtOAc); R_f 0.24 (3% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.88 (s, C(O)CH₃), 4.27 (d, J = 5.6 Hz, CH₂), 4.89-4.94 (dd, J = 6.4, 7.8 Hz, α-CH), 5.13-5.30 (m, -CH=CH₂), 5.81-5.93 (m, -CH=CH₂), 7.20-7.33 (m, 5 PhH), 8.27 (d, J = 7.8 Hz, NII), 8.58 (t, J = 5.6 Hz, NIH); ¹³C NMR (DMSO-d₆) 22.47 (C(O)CH₃), 42.05 (CH₂), 55.24 (α-CH), 116.44 (CH=CH₂), 126.74 (C_{4'}), 127.05 (2C_{2'} or 2C_{3'}), 128.24 (2C_{2'} or 2C_{3'}), 134.76 (CH=CH₂), 139.25 (C_{1'}), 168.78 (C(O)CH₃), 168.99 (C(O)NH) ppm.

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Example 127

1 *Synthesis of 2-Acetamido-N-benzyl-2-epoxyacetamide.* A solution of 2-acetamido-N-benzyl-2-vinylacetamide (1.00 g, 4.31 mmol) and m-chloroperoxybenzoic acid (1.76 g, 55%, 5.60 mmol) in dichloromethane (100 mL) was stirred at
5 room temperature (24 h), and then heated at reflux (3 h). The reaction solution was treated with a saturated aqueous Na_2SO_3 solution (20 mL) and then the organic layer was extracted with a saturated aqueous NaHCO_3 solution (3 x 50 mL). The organic layer was washed with a saturated aqueous NaCl solution and
10 dried (Na_2SO_4). The CH_2Cl_2 was removed *in vacuo*, and the residue was then purified by flash column chromatography on SiO_2 gel using 4% MeOH/EtOAc as the eluant to give 0.35 g (33%) of the desired product: mp °C (recrystallized from EtOAc); R_f 0.48 (5% MeOH/CHCl₃); ¹H NMR (DMSO-d₆) δ 1.87 (s, C(O)CH₃), 2.66 (dd, *J* = 2.5, 5.0 Hz, CH(O)CHH), 2.75 (dd, *J* = 4.3, 5.0 Hz, CH(O)CHH), 3.20 (m, CH(O)CHH), 4.25-4.32 (m, α-CH, CH₂), 7.21-7.34 (m, 5 PhH), 8.30 (d, *J* = 8.1 Hz, NH), 8.59 (t, *J* = 5.8 Hz, NH); ¹³C NMR (DMSO-d₆) 22.18 (C(O)CH₃), 41.99 (CH₂),
15 43.91 (CH(O)CH₂), 51.30 (CH(O)CH₂), 53.80 (α-CH), 126.49 (C_{4'}), 126.83 (2C_{2'} or 2C_{3'}), 127.98 (2C_{2'} or 2C_{3'}), 138.86 (C_{1'}), 168.52 (C(O)NH), 169.24 (C(O)CH₃) ppm.

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Example 128

1 *Synthesis of Potassium 2-Acetamido-N-benzylacetamide-2-sulfonate.* A
solution of 2-acetamido-N-benzyl-2-(trimethylammonium)acetamide tetrafluoroborate (0.30 g, 0.85 mmol) and K₂SO₃ (0.68 g, 4.26 mmol) in H₂O (7.0 mL) was
5 heated at 50-55 °C (4 h). The solution was evaporated to dryness, and the residue
was extracted with hot MeOH (3 x 10 mL). The MeOH was removed *in vacuo* to
give a white solid (~30 mg): ¹H NMR (D₂O) δ 1.97 (s, C(O)CH₃), 4.33 (CH₂), 5.45
10 (CH), 7.19-7.28 (m, 5 PhH); ¹³C NMR (D₂O) 22.00 (C(O)CH₃), 43.41 (CH₂), 67.77
(CH), 127.18 (2C₂' or 2C₃'), 127.53 (C₄'), 128.83 (2C₂' or 2C₃'), 137.58 (C₁'), 166.02
(C(O)NH), 173.65 (C(O)CH₃) ppm.

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Example 129

1 *Synthesis of Ethyl 2-Acetamido-4-pentenoic acid ester.* Allyltrimethylsilane (4.09 g, 31.40 mmol) was added to a stirred solution of ethyl 2-acetamido-2-bromoacetate (1.76 g, 7.86 mmol) in dry THF (90 mL). After stirring (5 min), an 5 ethereal solution of ZnCl₂ (1 N, 12.2 mL, 12.2 mmol) was added and the stirring was continued (70 h). The THF was removed by distillation *in vacuo* and the residue that remained was treated with H₂O (50 mL). The aqueous mixture was extracted with CH₂Cl₂ (3 × 75 mL), the combined extract was dried (Na₂SO₄) and 10 concentrated to give 1.40 g (97%) of the desired product. The ester was purified by distillation *in vacuo* (65-70 °C, 0.3-0.8 torr) to give the desired product as a colorless oil: R_f 0.35 (3% MeOH/CHCl₃); ¹H NMR (CDCl₃) δ 1.25 (t, J = 6.8 Hz, OCH₂CH₃), 1.99 (s, C(O)CH₃), 2.44-2.60 (m, CH₂CH=CH₂), 4.17 (q, J = 6.8 Hz, OCH₂CH₃), 4.60- 15 4.66 (m, CH), 5.07-5.11 (m, CH₂CH=CH₂), 5.59-5.70 (m, CH₂CH=CH₂), 6.15 (br s, NH); ¹³C NMR (CDCl₃) 14.09 (OCH₂CH₃), 23.00 (C(O)CH₃), 36.46 (CH₂CH=CH₂), 51.58 (CH), 61.39 (OCH₂CH₃), 118.95 (CH₂CH=CH₂), 132.15 (CH₂CH=CH₂), 169.64 (C(O)CH₃), 171.74 (C(O)OCH₂CH₃) ppm; mass spectrum, m/e (relative intensity) 20 186 (M⁺+1, 2), 144 (19), 126 (7), 112 (31), 102 (73), 87 (18), 71 (100), 70 (89).

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Example 130

1 *Synthesis of 2-Acetamido-4-pentenoic acid.* Ethyl 2-acetamido-4-pentenoic
acid ester (1.20 g, 6.50 mmol) was dissolved in 90:5 EtOH:H₂O (40 mL), and then
5 KOH (1.50 g, 26.80 mmol) was added and the resulting solution stirred at room
temperature (48 h). The reaction was concentrated *in vacuo* and the residue
diluted with H₂O (15 mL) and then washed with Et₂O (2 × 30 mL). The aqueous
layer was then made acidic with 8.5% H₃PO₄ and extracted with EtOAc (3 × 75
mL). The combined organic layers were dried (Na₂SO₄), and evaporated *in vacuo*
10 to give 0.56 g (55%) of the desired product: mp 113-115 °C (recrystallized from
EtOAc); ¹H NMR (DMSO-d₆) δ 2.00 (C(O)CH₃), 2.43-2.65 (m, CH₂CH=CH₂), 4.36-
4.43 (m, CH), 5.19-5.30 (m, CH₂CH=CH₂), 5.84-5.98 (m, CH₂CH=CH₂), 8.29 (d, J =
15 7.7 Hz, NH), 12.78 (br s, OH); ¹³C NMR (DMSO-d₆) 22.35 (C(O)CH₃), 35.44
(CH₂CH=CH₂), 51.68 (CH), 117.70 (CH₂CH=CH₂), 134.07 (CH₂CH=CH₂), 169.27
(C(O)CH₃), 173.11 (CO₂H) ppm; mass spectrum, m/e (relative intensity) 158 (M⁺⁺ 1,
2), 139 (6), 116 (20), 112 (8), 74 (73), 70 (47), 42 (100).

Anal. Calcd for C₇H₁₁NO₃: C, 53.50; H, 7.06; N, 8.91. Found: C, 53.64; H,
20 7.15; N, 8.82.

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102/103

Example 131

1 *Synthesis of 2-Acetamido-4-pentenoic acid-N-benzylamide.* 4-Methylmorpholine (0.55 g, 5.40 mmol) was added to a cooled (-10 to -15 °C) THF solution (60 mL) of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol), and then isobutylchloroformate (0.75 g, 5.70 mmol) was added leading to the precipitation of a white solid.
5 After 2 min, a solution of benzylamine (0.61 g, 5.70 mmol) in THF (10 mL) was slowly added at -10 to -15 °C. The reaction was allowed to warm (5 min) at room temperature and the insoluble salts were removed by filtration, and the filtrate
10 was evaporated to dryness. The residue was triturated with EtOAc (10 mL), and the remaining white solid was filtered to give 0.81 g (64%) of the desired product:
mp 118-120 °C (recrystallized from ethyl acetate/cyclohexane); R_f 0.36 (4% MeOH/CHCl₃); IR (KBr) 3200 (br), 3040, 2900, 1650 (br), 1540 (br), 1350, 750, 700
15 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.83 (s, C(O)CH₃), 2.22-2.49 (m, CH₂CH=CH₂), 4.26 (d,
 J = 5.3 Hz, CH₂Ph), 4.25-4.33 (m, CH), 4.99-5.09 (m, CH₂CH=CH₂), 5.65-5.77 (m,
CH₂CH=CH₂), 7.21-7.29 (m, 5 PhH), 8.05 (d, J = 7.6 Hz, NH), 8.46 (br s, NH); ¹³C
20 NMR (DMSO-d₆) 22.41 (C(O)CH₃), 36.24 (CH₂CH=CH₂), 41.91 (CH₂Ph), 52.20 (CH),
117.15 (CH₂CH=CH₂), 126.54 (C_{4'}), 126.99 (2C_{2'} or 2C_{3'}), 128.04 (2C_{2'} or 2C_{3'}), 139.22
(C_{1'}), 134.25 (CH₂CH=CH₂), 169.02 (C(O)CH₃), 170.96 (C(O)NH) ppm; mass
25 spectrum, m/e (relative intensity) 246 (M⁺, 4), 205 (4), 163 (15), 140 (8), 106 (33), 91
(77), 70 (100).

Anal. Calcd for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.55;
H, 7.31; N, 11.48.

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XAB JAH

Example 132

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Using the procedures described herein, the
following compounds can also be synthesized:

α -acetamido-N-benzyl-2-(2-oxazole)-acetamide

α -acetamido-N-benzyl-2-(2-thiazole)-acetamide.

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Pharmacology. Using male Carworth Farms #1 mice, compounds of the present invention were tested for anti-convulsant activity according to the following procedure:

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XCK/VGK

1 In the rotorod test, the animal was placed on a
one-inch diameter knurled plastic rod rotating
at 6 rpm after the administration of the drug. Normal
mice can remain on a rod rotating at this speed indefinitely.
5 Neurologic toxicity was defined as the failure of the
animal to remain on the rod for one minute. In the
horizontal screen test, previously trained mice were
dosed with the compound and placed individually on
top of a square (13 cm X 13 cm) wire screen (no. 4
10 mesh) which was mounted on a metal rod. The rod was
rotated 180°, and the number of mice that returned
to the top of the screen was determined. Inability
to climb to the top within one minute was defined as
15 "neurological impairment". This procedure is described
in Pharmacol. Biochem. Behav. 6, 351-353 (1977) and
is incorporated herein by reference with the same force
and effect as if fully set forth herein.

The dose effect behavior of the compounds was evaluated using
20 the above-described procedures by the administration
of varying dose levels, treating normally eight mice
at each dose. Table I includes an evaluation of the
Median Effective Dose (ED50) and the Median Toxic Dose
(TD50) of representative compounds. Mice were tested
25 with varying doses of the anticonvulsant to define
the limits of complete protection (or toxicity) and
no protection (or no toxicity), as well as three points
in between these limits. The Median Effective Dose
(ED50) was defined as the dose which produced the desired
30 endpoint in 50% of the animals. The Median Toxicity
Dose (TD50) was the dose which elicited evidence of
minimal neurological toxicity in 50% of the animals.

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More specifically, data tabulated in Table 1 were generated as follows:

The compound was given in various dose levels (i.e., 5 10, 30, 100, 300 mg) and subsequently compared with phenytoin, phenobarbital, mephenytoin and phenacetamide (See Table I). N-Acetyl-D,L-alanine-N'-benzylamide was tested at 600 mg/mL as well. Seizures were then artificially induced by either electroshock or pentylenetetrazole. Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50mA intensity (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 sec via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. The Subcutaneous Pentylenetetrazole (Metrazol^R) Seizure Threshold Test (sc Met) entailed the administration of 85 mg/kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline. This amount of pentylenetetrazole was expected to produce seizures in greater than 95% of mice. The animal was observed for 30 minutes. Protection was defined as a failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 sec duration). The results of these tests are tabulated in Table I.

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TABLE I

Comparative Median Effective Dosage

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	<u>Compound</u>	Tox	MES	sc Met
		<u>TD50 mg/kg</u>	<u>ED50 mg/kg</u>	<u>ED50 mg/kg</u>
	N-acetyl-D,L-alanine-N'-benzylamide	454 (417-501)*	77 (67-89)*	#
10	N-acetyl-D-alanine-N'-benzylamide	214 (148-262)*	55 (50-60)*	55 (43-67)*
	N-acetyl-L-alanine-N'-benzylamide	841 (691-594)*	548 (463-741)*	#
15	N-acetyl-D,L-phenylglycine-N'-benzylamide	>> 40	32.1	#
	N-acetyl-D-phenylglycine-N'-benzylamide	>> 80	26.4	#
20	N-acetyl-L-phenylglycine-N'-benzylamide	100-300	> 300	#
	D,L- α -acetamido-N-benzyl-3-thiophene-acetamide	> 100	87.80	#
25	D,L- α -acetamido-N-benzyl-2-thiophene-acetamide	30-100	44.80	#
	D,L- α -acetamido-N-benzyl-2-furan-acetamide	40	10.33	#
30	D,L- α -acetamido-N-benzyl-2-pyrrole-acetamide	< 100	16.10	#

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(Qd)

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TABLE I - cont'd.
Comparative Median Effective Dosage

	<u>Compound</u>	Tox <u>TD50</u> <u>mg/kg</u>	MES <u>ED50</u> <u>mg/kg</u>	sc Met <u>ED50</u> <u>mg/kg</u>
5	D,L-2-acetamido-N-benzyl-2-ethoxyacetamide	> 112	62.01	#
10	D,L-2-acetamido-N-benzyl-2-methoxyacetamide	< 300	98.30	#
15	(D,L)- α -Acetamido-N-benzyl-2-(5-methylfuran)acetamide	75.4 ^{XX}	19.2 (16.4-23.8)*	#
20	(D,L)- α -Acetamido-N-benzyl-2-benzofuranacetamide	>100<300 ^{XX}	>100<300	#
	(D,L)- α -Acetamido-N-benzyl-2-benzo[b]thiopheneacetamide	>100<300 ^{XX}	>100<300	#
25	(D,L)- α -Acetamido-N-(2-fluorobenzyl)-2-furanacetamide	x	36.5 (30.6-57.1)*	#
	(D,L)- α -Acetamido-N-(3-fluorobenzyl)-2-furanacetamide	x	40.0	#
30		135.6 (114.9-161.8) ^{XX}	13.3 (11.5-15.3)*	#

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	Tox TD 50 mg/kg	MES ED 50 mg/kg	scMet ED 50 mg/kg
16	2-acetamido-N-benzyl-2-aminoacetamide	† 65.1 (56.2-75.3)	†
5	2-acetamido-N-benzyl-2-(1-Pyrrolyl) acetamide	† 80.2	†
	2-acetamido-N-benzyl-2-(1-imidazolyl) acetamide	† >100	†
10	2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide	† 45.3	†
	2-acetamido-N-benzyl-2-(4-morpholine)acetamide	† >30, <100	†
	2-acetamido-N-benzyl-2-(N,N,N-trimethylammonium) acetamide tetrafluoroborate	† >100	†
	2-acetamido-N-benzyl-2-(N-anilino)acetamide	† >300	†
20	2-acetamido-N-benzyl-2-(N-(3-pyrazolylamino)) acetamide	† ~100	†
	2,2-diacetamido-N-benzyl-acetamide	† >100, <300	†
	2-acetamido-N-benzyl-2-trifluoroacetamidoacetamide	† >300	†
25	2-acetamido-N-benzyl-2-(N-hydroxyamino)acetamide	† ~100	†
	2-acetamido-N-benzyl-2-(N-methoxyamino)acetamide	46.0xx (38.0-56.0)	6.2 (5.4-7.2)
30	2-acetamido-N-benzyl-2-(N-(N-methylhydroxyamino)) acetamide	† ~30	†
	2-acetamido-N-benzyl-2-(N-(N,O-dimethylhydroxyamino)acetamide	50.5xx (40.4-59.9)	6.7 (5.7-7.7)
35	2-acetamido-N-benzyl-2-(N-isoxazolidino)acetamide	† 31.4 (26.7-37.8)	†

1	2-acetamido-N-benzyl-2-(N ² -phenylhydrazino)acetamide	†	~100	†
5	2-acetamido-N-benzyl-2-(N ² -benzyloxycarbonylhydrazino)acetamide	†	55.6 (49.3-63.9)	†
	2-acetamido-N-benzyl-2-hydroxyacetamide	†	80.1 (70.6-91.0)	†
10	2-acetamido-N-benzyl-2-(1-Pyrazoyl) acetamide	†	16.5 (14.1-22.5)	†
	2-acetamido-N-benzyl-2-phenoxyacetamide	†	>100	†
15	2-acetamido-N-benzyl-2-(methylmercapto)acetamide	†	>100	†
	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide	†	>30, <100	†
20	2-acetamido-N-benzyl-2-(S-thiophenoxy)acetamide	†	>300	†
	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomer A)	†	>100	†
25	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomers A + B)	†	>100	†
	2-acetamido-N-benzyl-2-(ethylsulfonyl)acetamide	†	>100	†

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~6V

1	(D,L)- α -Acetamido-N-(4-fluorobenzyl)-2-furan-acetamide	144.4 (122.5-170.9) XX	12.7 (10.4-15.1)*
5	(D,L)- α -Acetamido-N-(2,5-difluorobenzyl)-2-furan-acetamide	x	23.8 (20.2-28.4)*
	(D,L)- α -Acetamido-N-(2,6-difluorobenzyl)-2-furan-acetamide	x	
10	(D, L)- α -Acetamido-N-benzyl-2-furanacetamide	23.8 XX	>25<100
	(L)-(+)- α -Acetamido-N-benzyl-2-furanacetamide	-	3.3 (2.8-3.9)*
15	(D,L)-2-Acetamido-4-pentenoic acid-N-benzylamide	>300	>100<300
	2-acetamido-N-benzyl-2-(2-Pyridyl) acetamide	x	33.6
20	(D,L)-2-Acetamido-N-benzyl-2-(methylamino)acetamide	95.0	8.5
	(D,L)-2-Acetamido-N-benzyl-2-(ethylamino)acetamide	x	44.5 (37.0-52.4)*
25	(D,L)-2-Acetamido-N-benzyl-3-indoleacetamide	x	42.4 (37.2-47.8)*
	phenytoin	x	xxx
	phenobarbital	66	10
30	mephentytoin	69	22
	phenacemide	154	61
	421 (337-549)*	87 (74-100)*	31
	95% confidence intervals:		116 (71-150)*

* For x The TD50 for this substrate was not computed.

xx The TD50 value was determined using the horizontal screen test.

xxx No activity was noted at \leq 300 mg/kg

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Other results from the pharmacological protocols
are summarized in Tables II, III and IV.

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Table II Selected Physical and Pharmacological Data In Mice for α -Acetamido-N-benzyl-2-furanacetamide (2)-Derivatives.^a

5	CMP#	Ra	Rb	Rc	$\text{CH}_3\text{CNH}-\overset{\text{X}}{\underset{\text{Rb}}{\text{C}}}-\overset{\text{Rc}}{\underset{\text{Y}}{\text{C}}}-\text{NHR}_e$		mp ^b	MES ^c ED ₅₀ mg/kg	Tox ^d TD ₅₀ mg/kg	PI
					X	Y				
	3a		H	CH ₂ C ₆ H ₅	O	O	159-161	51.7 (44.4-59.9)	t	-
10	3b		H	CH ₂ C ₆ H ₅	O	O	130-132	89.8 (78.4-103.4)	t	-
	4		CH ₃	CH ₂ C ₆ H ₅	O	O	-	>300	t	-
	5		H	CH ₂ C ₆ H ₅	S	O	78-80	18.4 (15.9-22.0)	t	-
	6		H	CH ₂ C ₆ H ₅	S	S	99-101	>100	t	-
15	7		H	CH ₂ -	O	O	172-174	>30	t	-
	8		H	CH ₂ -	O	O	168-170	>100	t	-
20	9		H	CH ₂ -	O	O	159-161	>30	t	-
	10		H	CH ₂ -	O	O	210-212	>100	t	-

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Table II continued

1	11		H	NHNH- 	O	O	226-228	>100	f	
	12		H	CH ₂ - 	O	O	188-190	12.7 (10.4-15.1)	144 (123-171)	11.3
5	(R)-12		H	CH ₂ - 	O	O	205-207	3.5 (2.9-4.4)	14.4 (7.3-28.9)	4.1
	(R)-13		H	CH ₂ - 	O	O	210-212	<10	f	
	(R)-14		H	CH ₂ - 	O	O	193-195	>10,<30	f	
10	phenytoin ^a							9.5 (8.1-10.4)	65.5 ⁱ (52.5-72.1)	69
	phenobarbital ^b							21.8 (15.0-22.5)	69.0 ⁱ (62.8-72.9)	32
	valproate ^b							272 (247-338)	426 ⁱ (369-450)	1.6
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^aThe compounds were administered intraperitoneally. ED₅₀ and TD₅₀ values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. ^bMelting points (°C) are uncorrected. ^cMES = maximal electroshock seizure test. Compound was suspended in 30% PEG. ^dTox = neurologic toxicity determined from horizontal screen unless otherwise noted. ^ePi = protective index (TD₅₀/ED₅₀). ^fNot determined. ^gThick oil.

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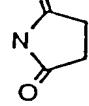
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T2070X

1 Table III Selected Physical and Pharmacological Data in Mice for N-Substituted α,α -Diamino Acid Derivatives.^a

no	R ²	$\text{CH}_3\text{CNH}-\text{CH}(\text{R}^2)-\text{C}(=\text{O})\text{NHCH}_2\text{Ph}$			tox ^d TD ₅₀
		mp ^b	MES ^c ED ₅₀		
2e	NHC(O)CH ₃	202-204	>30,<100		e
2f	NHC(O)OPh	201-203	>100		e
2g	NHC(O)NHCH ₃	229-230	>100		e
2h	NHC(O)NHPH	242-244	>100		e
2i	NHC(O)NHS(O ₂)Ph	188-191	>100		e
2j	NHC(S)NHCH ₃	162-163	>100		e
2k	NHC(S)NHPH	196-197	>100		e
2l	NHC(O)Ph(2'-CO ₂ H)	186-188	>100		e
2m		181-183	>100		e
2n	NHC(O)CH ₂ NHC(O)OCH ₂ Ph	177-179	>10,<30		e
2o	NHCH ₂ C(O)OCH ₂ CH ₃	125-127	>100		e
2p	NHCH ₂ C(O)OCH ₂ Ph	133-135	72		74

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Table III continued

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 NH₂CH₂CO₂⁻

124-126

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phenytoin

95
(8.1-10.4) 65.5^f
(52.5-72.1)

phenobarbital

21.8
(15.0-22.5) 69.0^f
(62.8-72.9)

valproate

272
(247-338) 426^f
(369-450)

10

^aThe compounds were administered intraperitoneally. ED₅₀ and TD₅₀ values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. ^bMelting points (°C) are uncorrected. ^cMES = maximal electroshock seizure test. Compound was suspended in 30% PEG unless otherwise noted. ^dTox = neurologic toxicity determined from horizontal screen unless otherwise noted. ^eNot determined. ^fNeurologic toxicity determined using the rotarod test.

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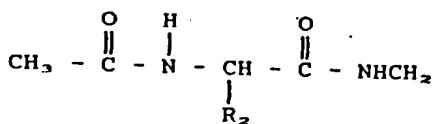
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Table IV Pharmacological Data in Mice for α -Acetamido-N-Benzyl-2-Heterocyclic Derivatives

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	<u>R₂</u>	<u>MES^a ED₅₀</u>	<u>tox^b TD₅₀</u>
		80.2	--
10		16.5	66.9 (55.6-81.1)
		>100	--
15		>30, <100	--
		>300	
		>100	--
20		>100	>100
		>100	--
25		>100	--

^a MES = maximal electroshock seizure test. Compound was suspended in 30% PEG.

^b TOX = neurologic toxicity determined from horizontal screen unless otherwise noted.

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Thus, while the invention has been described with reference to certain preferred embodiments, those skilled in the art will realize that changes and modifications may be made thereto without departing from the full and intended scope of the appended claims.

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